FENWAY HEALTH



GENDER-AFFIRMING HORMONE THERAPY

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fenwayhealth.org

GOALS AND OBJECTIVES

1. Review process of initiating hormone therapy through the informed consent model

2. Provide an overview of masculinizing and feminizing hormone therapy

3. Review realistic expectations and benefits of hormone therapy vs their associated risks

4. Discuss recommendations for monitoring

PROTOCOLS AND STANDARDS OF CARE



WPATH STANDARDS OF CARE, 2011

The criteria for hormone therapy are as follows:

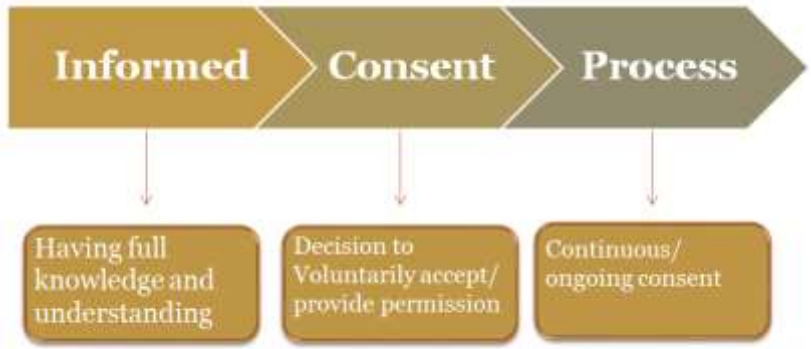
1. Well-documented, persistent (at least 6mo) gender dysphoria
2. Capacity to make a fully informed decision and to consent for treatment
3. Age of majority in a given country
4. If significant medical or mental health concerns are present, they must be *reasonably well controlled*

INFORMED CONSENT MODEL

- Requires healthcare provider to
  - Effectively communicate benefits, risks and alternatives of treatment to patient
  - Assess that the patient is able to understand and consent to the treatment

- Informed consent model does not preclude mental health care!
- Recognizes that prescribing decision ultimately rests with clinical judgment of provider working *together* with the patient

- Recognizes patient autonomy and empowers self-agency
- Decreases barriers to medically necessary care



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INITIAL VISITS

- Review history of gender experience and patient's goals
- Document prior hormone use
- Assess appropriateness for gender affirming medical treatment
  - WPATH criteria
  - Assess social support system and safety
- Assess medical safety
  - CPE / thorough medical history
    - Consider specific contexts that increase risk and health disparities in the population
  - Obtain sexual history
  - Order screening laboratory studies
- Provide informed consent
  - Review risks and benefits of hormones therapy
- Provide referrals

FENWAY HEALTH



LABORATORY MONITORING

BASELINE

Transmasculine

- **CBC (Hgb/Hct)**
- Lipid Profile, *only as clinically indicated*
- Fasting Glucose, *only if clinically indicated*
- Liver Enzymes, *only if evidence of underlying liver disease*
- Screen for PCOS with +ROS, *??*



Transfeminine

- **Baseline kidney function**
- Lipid Profile, *only as clinically indicated*
- Fasting Glucose, *only if clinically indicated*
- Liver Enzymes, *only if evidence of underlying liver disease*

GENDER-AFFIRMING HORMONE THERAPY

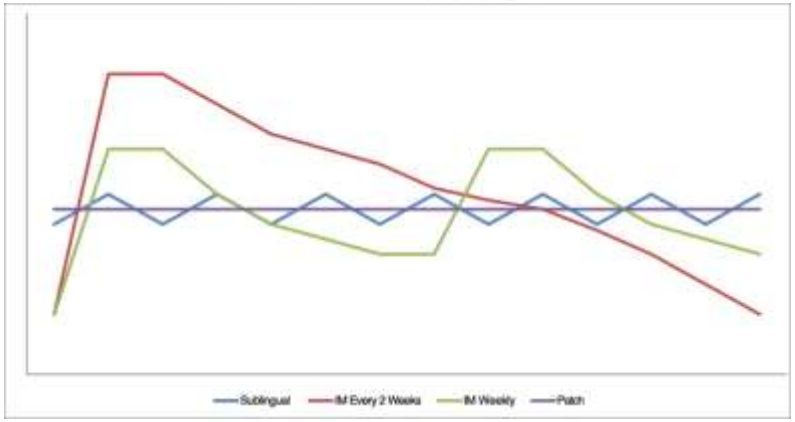
MASCULINIZING HORMONE OPTIONS

Injectable Testosterone

- Testosterone Enanthate or Cypionate IM or SC, q1 or 2 weeks



- **Weekly Dosing versus Biweekly Dosing**
  - Consider susceptibility of peak/trough levels with biweekly dosing. Consider mental health diagnosis



- **Standard Weekly Dose:** 50 – 100 mg / week
  - Starting at 50mg/week and increase in 1 month
- **Standard Biweekly Dose:** 150-200 mg / 2 weeks
  - Starting with 100mg/biweekly and increase in 1 month

TRANSDERMAL TESTOSTERONE

- **Patches**
  - Androderm: (2 & 4mg patches) Apply 2-8mg/day



- **Topical gels in packets and pumps**
  - Apply 50 – 100mg/day
  - Androgel pump: 1.62% gives 20.25mg per pump
    - 2 pumps for starting dose
  - Androgel or Testim packets: 25mg (2.5gm) or 50mg (5gm)
    - Generally start with 50mg packet
    - Intended to be applied to Arm > Abdomen > Inner thigh
  - Axiron 2% pump gel for axillary application: 1 pump (30mg) to each axilla daily





OTHER OPTIONS

Testosterone Pellet

- Testopel - Implant 8-12 pellets q 3 to 4 months



Testosterone undecanoate

- AVEED - Injectable long-acting. 750mg/3mL injection every 10wks, with initial loading dose



ADDITIONAL MEDICATIONS

- **Testosterone cream/DHT cream** for clitoral enlargement
- **Estrogen vaginal cream** for atrophy of the frontal canal
  - Also can be used for inadequate pap tests
- **Rogaine or Finasteride** for male pattern baldness
- **Progesterone – LARC (IUD, Nexplanon), Depo**, which may aid in cessation of menses before or after starting testosterone therapy

TIMELINE FOR MASCULINIZING EFFECTS

Effect	Onset (months)	Maximum (years)
Skin oiliness/acne	1-6	1-2
Fat redistribution	1-6	2-5
Cessation of Menses	2-6	
Clitoral enlargement*	3-6	1-2
Vaginal atrophy	3-6	1-2
Emotional changes		
Increased sex drive		

CONTINUED…



Effect	Onset (months)	Maximum (years)
Deepening of voice*	3-12	1-2
Facial/Body Hair Growth*	6-12	4-5
Scalp Hair Loss*	6-12	
Increased Muscle Mass & Strength	6-12	2-5
Coarser Skin/ Increased Sweating		
Weight Gain		
Mild Breast Atrophy		
Tendon Injury		

RISKS OF TESTOSTERONE THERAPY

- Lower HDL & Elevate TG
- Polycythemia/erythrocytosis
- Limited long-term data: breast, endometrial tissue, ovarian tissue
  - Good short-medium term data!
- Increased risk of sleep apnea
- Increase insulin resistance?
- Infertility
- Pelvic pain
- Mental health effects
- Hepatotoxicity (with oral formulations)
  - Much less risk with parenteral formulations



FOLLOW UP LAB MONITORING

Serum testosterone levels

- At 6 and 12 months, then as clinically indicated
- If using topical, consider checking testosterone level at 3 months
- May be checked 6 to 12 weeks after dosage change
- Goal Range: ~350-900 ng/dl



Estradiol levels?

Goal Range: less than 50 pg/ml

- Do not need to check if T in therapeutic range.
- Only check if not masculinizing, abnormal bleeding, etc.

FOLLOW UP LAB MONITORING

After 6 months → then every 6 to 12 months

- Hct/Hgb
- Lipid Profile, as clinically indicated
- Fasting Glucose or HbA1c, as clinically indicated
  - Testosterone may impact glucose metabolism, increasing insulin resistance



FEMINIZING HORMONE OPTIONS

Oral Estrogens

- Estradiol (estrace) 2-8 mg PO or SL daily (can be divided into BID dosing)
- Premarin (conjugated estrogens) 1.25-10mg PO daily (can be divided into BID dosing)



Injectable Estrogens

- Estradiol valerate 5-20mg IM q2 weeks
- Estradiol cypionate 2-10mg IM weekly



Transdermal Estrogens

- Estradiol patch 0.1-0.4mg twice weekly, may start lower in patients at risk of side effects. Maximum single dose patch available is 0.1 mg





ANTIANDROGENS



- **Spironolactone** (aldactone) 50-400mg PO daily (can be divided into BID dosing)
- 5-alpha reductase inhibitors: finasteride (Proscar) and dutasteride - Inhibits conversion of testosterone to DHT
- Casodex (bicalutamide) - non-steroidal androgen receptor inhibitor
- Lupron $$$ - Leutinizing hormone (LH) releasing hormone agonist, more simply called a GnRH agonist
- Cyproterone acetate - synthetic progestagen with strong anti-androgen activity

WHAT ABOUT PROGESTINS?

Most often requested for:

- Benefit on breast development
- Part of the "natural" female hormonal make-up

Potential Risks

- Associated with increased risk of cardiovascular events and breast cancer in WHI
  - But, how does this translate to trans women?
- Weight gain and depression
- No clear evidence of affect on breast growth!

Potential Benefits

- Weight gain!, moodiness!/cycling
- Improved mood
- Improved libido, energy
- Anti-androgen effect?

BREAST DEVELOPMENT IN TRANS WOMEN

J Sex Med. 2014 May;11(5):1240-7. doi: 10.1111/jsm.12487. Epub 2014 Mar 12.

Clinical review: Breast development in trans women receiving cross-sex hormones.

Wierckx K[1], Gooren L, T'Sjoen G.

- 11 studies, just under 1000 patients
- Only 3 studies with more than 100 subjects
- Generally poor quality studies. How to objectively measure the breast? Many used subjective measures of breast satisfaction or wish for breast augmentation

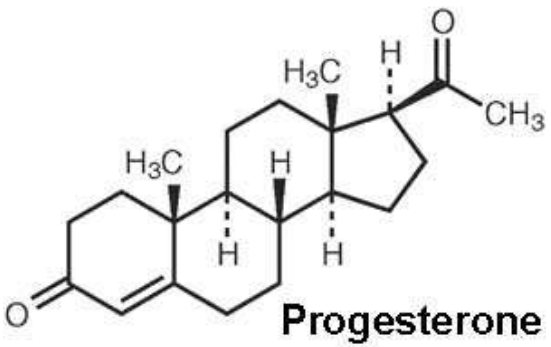
CONCLUSIONS:

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast development in trans women is extremely sparse and based on low quality of evidence. **Current evidence does not provide evidence that progestogens enhance breast development in trans women. Neither do they prove the absence of such an effect.** This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions.

PROGESTINS

- **Prometrium 100 mg – 200 mg po daily***
- Provera 2.5 to 10 mg PO daily
- Depo-Provera 150 mg IM q 3 months

Consider daily vs cyclic administration of oral progestin: 10 days each month, to lower total exposure to progestin and/or to more closely mimic female physiology



Progesterone

FEMINIZING EFFECTS OF ESTROGENS & ANTIANDROGENS

Effect	Onset (months)	Maximum (months)
Decreased Libido	1-3	3-6
Decreased Spontaneous Erections		
Breast Growth*	3-6	24-36
Decreased Testicular Volume*	3-6	24-36
Decreased Sperm Production*	Unknown	Unknown
Redistribution of Body Fat	3-6	24-36
Decrease in Muscle Mass	3-6	12-24
Softening of Skin	3-6	Unknown
Decreased Terminal Hair	6-12	>36

NOTE: Possible slowing or cessation of scalp hair loss, but no regrowth

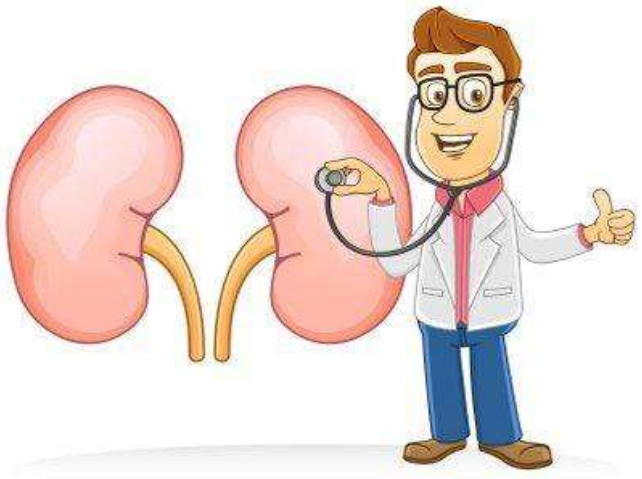
- No change in voice

RISKS OF ESTROGEN THERAPY

- Venous thrombosis/ thromboembolism
- Increased risk of cardiovascular disease
- Weight gain
- Decreased libido
- Hypertriglyceridemia
- Elevated blood pressure
- Decreased glucose tolerance
- Gallbladder disease
- Benign pituitary prolactinoma
- Mental health effects
- Infertility

RISKS OF SPIRONOLACTONE THERAPY

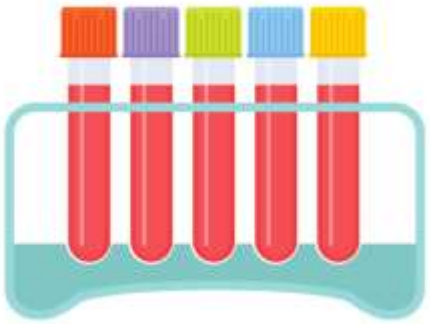
- Increased urinary frequency
- Hypotension
- Hyperkalemia
  - Co-administration with ACE inhibitor or ARB
- Dehydration and renal insufficiency
  - Co-administration with HCTZ



LAB MONITORING FOR TRANS FEMININE PATIENTS

- Serum testosterone level (at 6 to 12 months)
  - Should be less than 55 ng/dl

- Serum Estradiol Levels
  - Target serum level seems to be the mean daily level for premenopausal cis-gender women (about 100 to 200 pg/ml)
  - Timing of blood draw?



LAB MONITORING FOR TRANS FEMININE PATIENTS

- If on spironolactone —
  - BUN/Cr and serum electrolytes 2 to 6 weeks after start/dosage change
  - every 3 months in first year
  - then yearly
- Lipids, glucose, LFTs only as clinically indicated
  - Prolactin level ?? vs only with +ROS
- Hgb/Hct will often drop into the normal female range in women on GAHT

FOLLOW UP CARE FOR GENDER-AFFIRMING HORMONE THERAPY

- Assess masculinization or feminization
  - Think about particular considerations for non-binary, gender fluid, and gender queer patients
    - Low dose hormones, surgery w/o hormones, short term hormone use, etc
- Review medication use
- Monitor mood and underlying behavioral health conditions
- Discuss social impact of transition
- Counsel regarding sexual activity
  - Remember that this can change! Sexual orientation, experimentation, increased confidence, increased libido
- Review surgical options
- Plans change of name and gender marker on legal forms
- Review CAD risk factors
- ASSESS SAFETY

NON-BINARY INDIVIDUALS

- Adjust doses of spironolactone and/or estradiol to maintain testosterone levels in a range between standard male and female levels
- Use of anti-androgens alone
- Limited courses of hormone therapy
- Surgical affirmation without hormone treatment



HORMONE THERAPY AND AGING

- Many gender diverse individuals start gender-affirming therapy at later ages; may experience slower and less vigorous changes
- Co-occurring medical issues may increase risk
- No clinical evidence to guide us on how long to continue hormone therapy
- Consider lowering dose of estrogen or testosterone around age 50, if patient has been on therapy for a number of years. Likely little benefit in stopping — maybe 65??



Questions?



Case 1



- J is a 24yo AFAB gender queer individual on gender-affirming testosterone therapy for the past 2-3 years. Referred to me for Testopel insertion, as they cannot tolerate self-injection

- Needlephobia leading to missed doses, which then worsens anxiety and dysphoria

- Reports they have been on topical gel in the past, but would experience occasional breakthrough bleeding/spotting due to poor absorption/low levels. Menses causes LOTS of dysphoria

- In talking about the above, they say, "Really the only reason I'm on higher levels of T is to stop the bleeding. Testosterone is important for me, but lower levels would probably be more affirming"

What are their options?

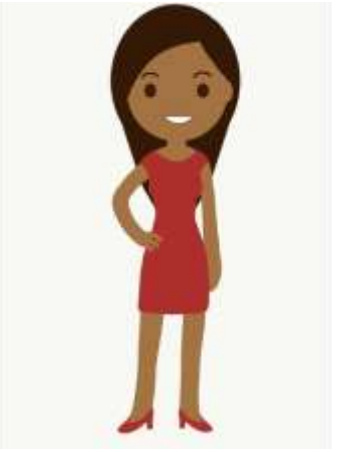
Case 1



- **Cessation of menses**
  - Progesterone: LARCs (Nexplanon, IUD), norethindrone acetate
    - Risk of spotting and/or irregular menses with LARCs, but much less likely when taken in conjunction with T
    - Discuss that these medications are used for lots of indications, not just birth control!

- **Low dose testosterone**
  - Gels are great for this! — Low dose, daily vs every other day. Easy to stop and/or adjust.
  - Testopel is long-acting and can lead to high peaks. More unpredictable. Once it's in, it's in!

Case 2



- P is a 26yo trans feminine individual on oral estrogen and spironolactone therapy for the past 2 years. Has found GAHT affirming, but is frustrated with persistent spontaneous erections. Also feels her breast growth is not as profound as she had hoped
- Despite titrating up on P's estradiol from 4mg initially to 8mg daily currently, her estradiol level has never been higher than 70pg/mL
- She is also on spironolactone 100mg twice daily and her total testosterone level is consistently between 300-500ng/dL
- You have no doubt she is taking her medications regularly. She is otherwise healthy and does not take any other medications

What are her options?

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Transgender Health
Mary Ann Liebert, Inc. publishers

ORIGINAL ARTICLE Open Access

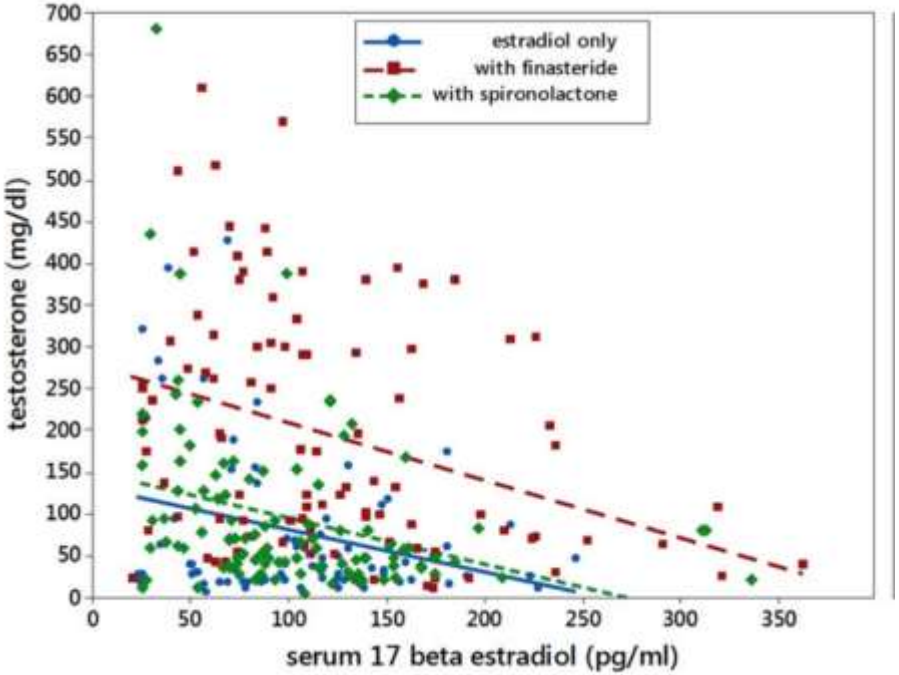
Hormonal Treatment of Transgender Women with Oral Estradiol

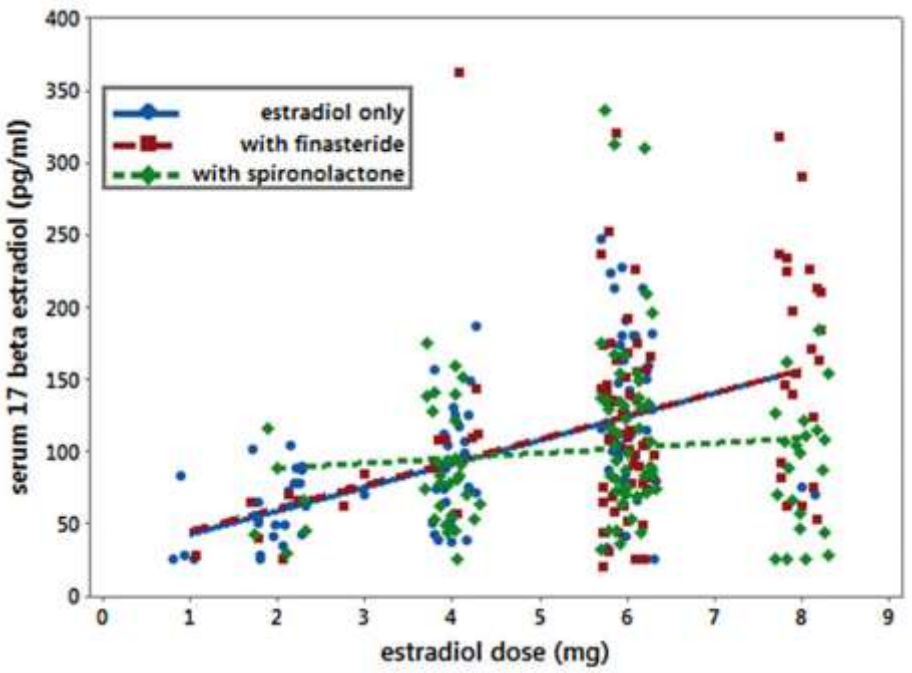
Matthew C. Leinung,[1,*] Paul J. Feustel,[2] and Jalaja Joseph[1]

- 136 patients on 2-8mg oral estradiol alone, or in conjunction with spironolactone 100mg BID, or finasteride 5mg daily
- Avg age 37, BMI 28
- Goal was serum estradiol >100pg/mL and testosterone <100ng/dL
- Findings:
  - 18% did not achieve goal estradiol levels on 6mg daily. When increased to 8mg, 10% still not at goal (90% did achieve target levels)
  - 28% did not achieve serum T levels <100. Of those, 29% did not achieve goal with addition of medroxyprogesterone

Thought provoking findings!

- Estradiol appeared to inversely impact testosterone levels
- Spironolactone appeared to have NO statistically significant impact on testosterone levels
- Presence of spiro seemed to REDUCE the effectiveness of estradiol reaching desired serum levels





Interaction of spironolactone with oestradiol receptors in cytosol. Levy J, et al. 1980:

Spiro at high doses blocks androgen receptor, and may have some agonist activity effect on estrogen receptor. However, in the presence of estrogen, it behaved as a competitive inhibitor at the estrogen receptor.

Medroxyprogesterone Acetate in Gender-Affirming Therapy for Transwomen: Results From a Retrospective Study

J Clin Endocrinol Metab, November 2019, 104(11):5148–5156

Jaison Jain,[1,2,3] Daniel Kwan,[2,3] and Michelle Forcier[1,3]

- 290 follow-up visits of TW treated from January 2011 - July 2018
- Mean duration of therapy 3.4 +/- 1.7 years
- Regimens include Estradiol and Spironolactone, with MPA (n = 102) or without MPA (n = 188)

- **Main Outcome Measures**:
. Assessed incidence of self-reported effects after MPA treatment
. Compared blood levels of E, testosterone, and various laboratory parameters between MPA and non-MPA groups

- **Results**:
. Mean weighted E level was 211 +/- 57 pg/mL after MPA treatment and 210 +/- 31 pg/mL
. Mean weighted testosterone level was 79 +/- 18 ng/dL after MPA treatment and 215 +/- 29 ng/dL ** testosterone levels were significantly lower in the MPA group
.Of 39 patients receiving MPA, 26 reported improved breast development and 11 reported decreased facial hair
. Five patients experienced mood swings on MPA

- **Conclusions**: In our cohort of transwomen, we found minimal side effects, unchanged E levels, and a decline in testosterone associated with MPA

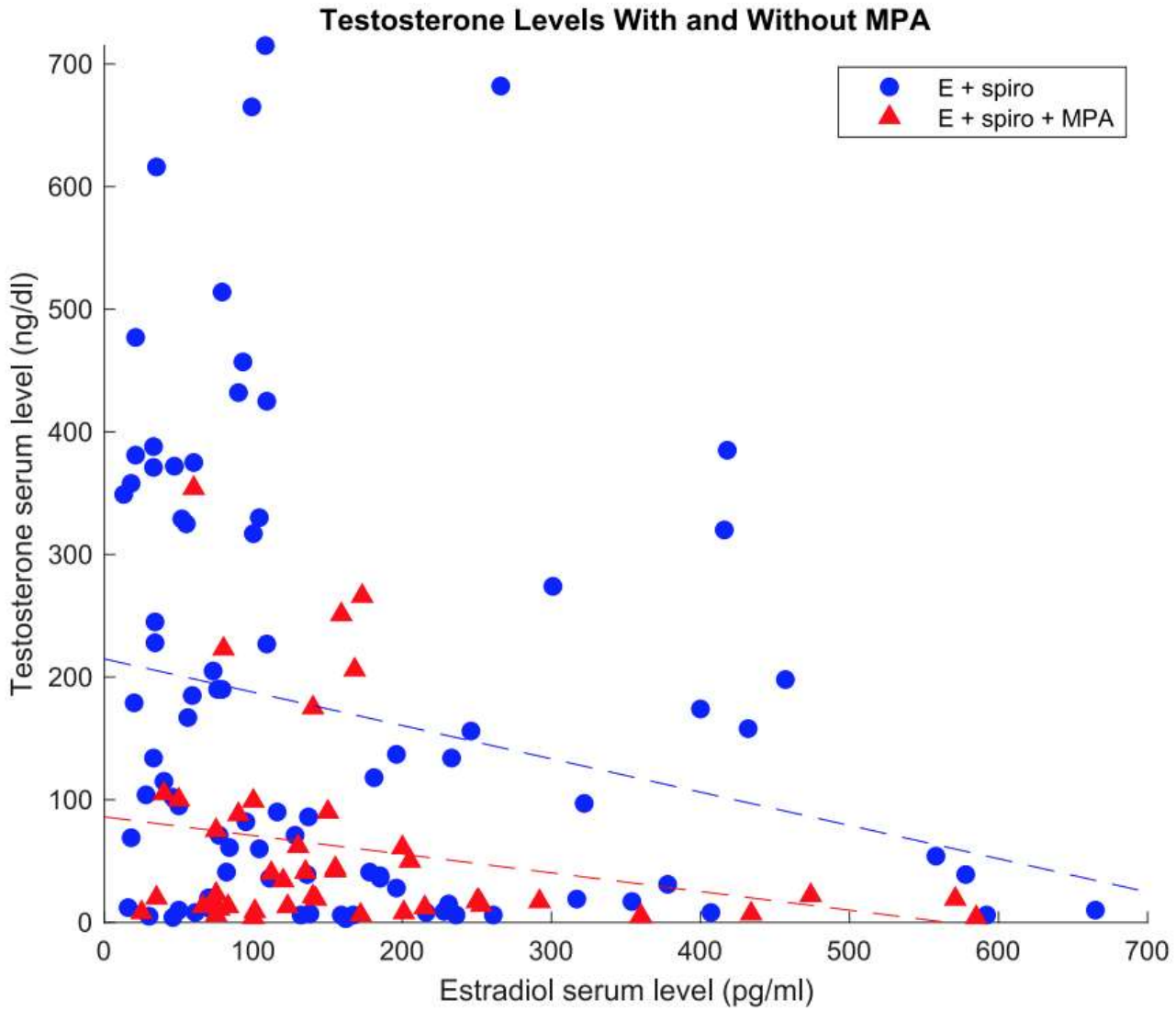


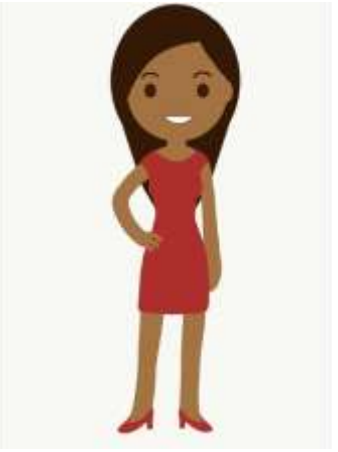
Figure 2. Total serum testosterone vs serum E in patients adhering to regimens of E and spironolactone (spiro), with or without MPA.

ANTIANDROGENS



- **Spironolactone** (aldactone) 50-400mg PO daily (can be divided into BID dosing)
- 5-alpha reductase inhibitors: finasteride (Proscar) and dutasteride - Inhibits conversion of testosterone to DHT
- Casodex (bicalutamide) - non-steroidal androgen receptor inhibitor
- Lupron $$$ - Leutinizing hormone (LH) releasing hormone agonist, more simply called a GnRH agonist
- Cyproterone acetate - synthetic progestagen with strong anti-androgen activity

Case 2



- **Increasing serum estrogen**
  - Perhaps she is over-metabolizing the oral — try another formulation:
    - Injectable. Peaks seem to be excellent at driving down testosterone levels on their own
    - Topical. Good absorption. Safe and effective. If can increase serum E, seems like that will suppress T

- **Decreasing serum testosterone**
  - Add progesterone. Perhaps anti-androgen effect through central blockage of gonadatropins
  - Add finasteride. Block conversion of remaining T to DHT
  - Lupron! Will require a PA, but will be effective.