NATIONAL LGBTQIA+ HEALTH EDUCATION CENTER

A PROGRAM OF THE FENWAY INSTITUTE

Project ECHO®

Estrogen Therapy and Anti-Androgens as Gender Affirming Hormone Therapy

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GOALS OF CARE

- Gender affirmation
  - What are the patient's priorities and goals?
    - Non-binary patients
    - Female-identified patients
  - What are the patient's particular medication requests or concerns and are these reasonable?

- Determining medications and dosing
  - Individualized — ALL people have varying amounts of hormones in their body
    - What is necessary for some, is not for others
    - What is safe for some, is not for others
    - Both physical and emotional responses to hormones vary
    - Consideration of underlying risks (family history, current co-morbidities, lifestyle)
    - Cost, insurance coverage, access, frequency, needle phobia …
    - Knows and unknowns in terms of short-term and long-term health!

September 2011 WPATH Standards of Care

- The criteria for hormone therapy are as follows:
  - Persistent, well-documented gender dysphoria;
  - Capacity to make a fully informed decision and to consent for treatment;
  - Age of majority in a given country (if younger, follow the Standards of Care outlined in section VI);
  - If significant medical or mental health concerns are present, they must be reasonably well controlled

Patients will try to get what they need

- Many patients have taken non-prescribed hormones
  - 2013 Ontario survey: 25% had ever used and 6.4% were currently using
  - 2009 NYC study: 23% of transwomen currently using
  - 2007 Virginia Trans Health Initiative Survey: 60% of transwomen and 23% of transmen had ever used
  - 2001 San Francisco Study: 29% of transwomen and 3% of transmen in the past 6 months
  - 2000 Washington, DC Transgender Needs Assessment Study: 58% had used at some time in the past

The Armamentarium

- Estrogens: PO, SL, IM, PR, Topical
  - Conjugated estrogens vs. estradiol vs. ethinyl estradiol via COCPs
    - Injectables
      - Estradiol valerate
      - Estradiol cypionate
- Progestins: PO, IM, PR
  - Progesterone
  - Medroxyprogesterone acetate
- Anti-Androgens
  - Androgen receptor blockers
  - 5-alpha-reductase inhibitors

Estrogen treatment

- **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
- **Topical Estrogens**
  - Divigel: 0.25mg-1.25mg/packet

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**
- Infertility
- Mental health effects
- ? Breast cancer

Risk of Adverse CV Outcomes in TGD People using Estrogen: 3 Studies from 2018

Study		MI	VTE	Stroke
Getahun et al "Kaiser study" CA and GA, USA	N=853	1.0 (0.3-3.2)	3.2 (1.5-6.5)	2.3 (1.2-4.3)
Nota et al Netherlands	N=872	1.16 (0.6-2.1)	3.39 (1.78-5.88)	2.5 (1.16-4.75)
Asscheman et al US and Europe	N=1248	0.75 (0.33-1.49)	3.0 (1.86-4.59)	1.05 (0.45-2.07)
Conclusion		No change	2-4x Increase	Unclear

Premarin vs. Estradiol

Nicholas L. Smith. **Lower Risk of Cardiovascular Events in Postmenopausal Women Taking Oral Estradiol Compared With Oral Conjugated Equine Estrogens**. *JAMA Internal Medicine*, 2013

- Current oral CEEs use compared with current oral estradiol use was associated with an increased venous thrombosis risk (odds ratio, 2.08; 95% CI, 1.02-4.27; P = .045)
- risk of having a heart attack was somewhat -- but not significantly -- higher in women using oral conjugated equine estrogens than in those using oral estradiol.
- No difference was seen in the risk of stroke.

Harm Reduction with Estrogen

- Stick with estradiol
- Avoid first-pass hepatic metabolism
  - SL, IM, topical
- Dose correctly to get into typical cis-female range
- Behavioral supports
  - Smoking cessation;
  - lipids and glucose management – diet;
  - exercise

Anti-androgens

- **Spironolactone** (aldactone) 50-400mg PO daily (can be divided into BID dosing)
- **Finasteride** (Proscar) 2.5-5mg PO daily
- **Bicalutamide (Casodex),** used in treatment of prostate CA; reports of severe liver toxicity: 50mg daily
- **GnRH agonist**: Goserelin Acetate, Leuprolide, Histrelin
- **Flutamide** an androgen receptor blocker, associated with severe liver toxicity (nonfatal aminotransferase elevations in 42–62% of)
- **Cyproterone Acetate** (not available in US)

Risks of Spironolactone Therapy

- Increased urinary frequency
- Hyperkalemia
- Hypotension and generalized weakness
- Renal insufficiency and dehydration

- ?? “Brain fog” ??
- Impact on breast development?

Case Reports > World J Gastroenterol. 2016 Apr 21;22(15):4062-5.
doi: 10.3748/wjg.v22.i15.4062.

Atypical onset of bicalutamide-induced liver injury

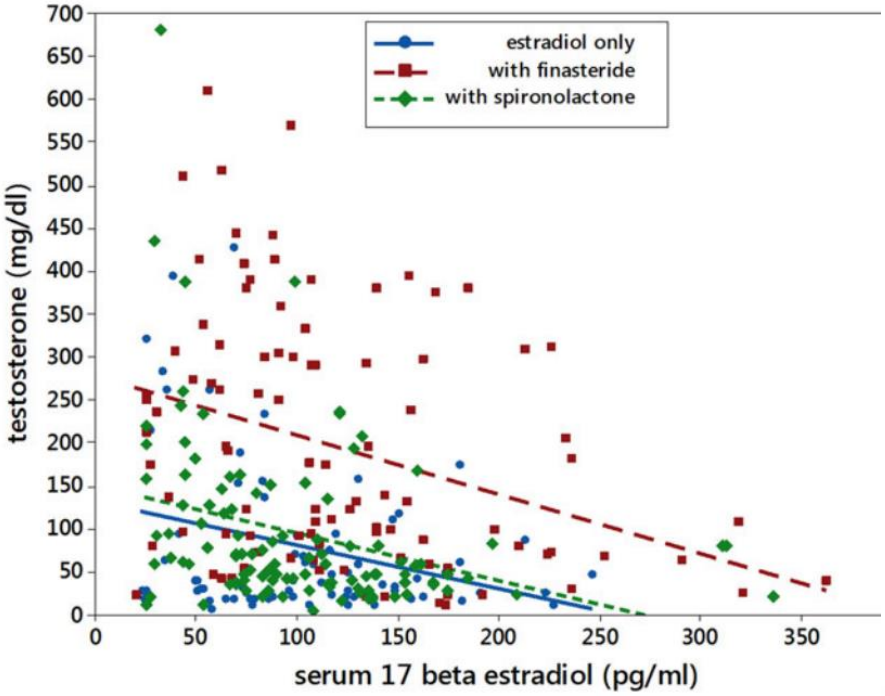
Gee Young Yun [1], Seok Hyun Kim [1], Seok Won Kim [1], Jong Seok Joo [1], Ju Seok Kim [1], Eaum Seok Lee [1], Byung Seok Lee [1], Sun Hyoung Kang [1], Hee Seok Moon [1], Jae Kyu Sung [1], Heon Young Lee [1], Kyung Hee Kim [1]

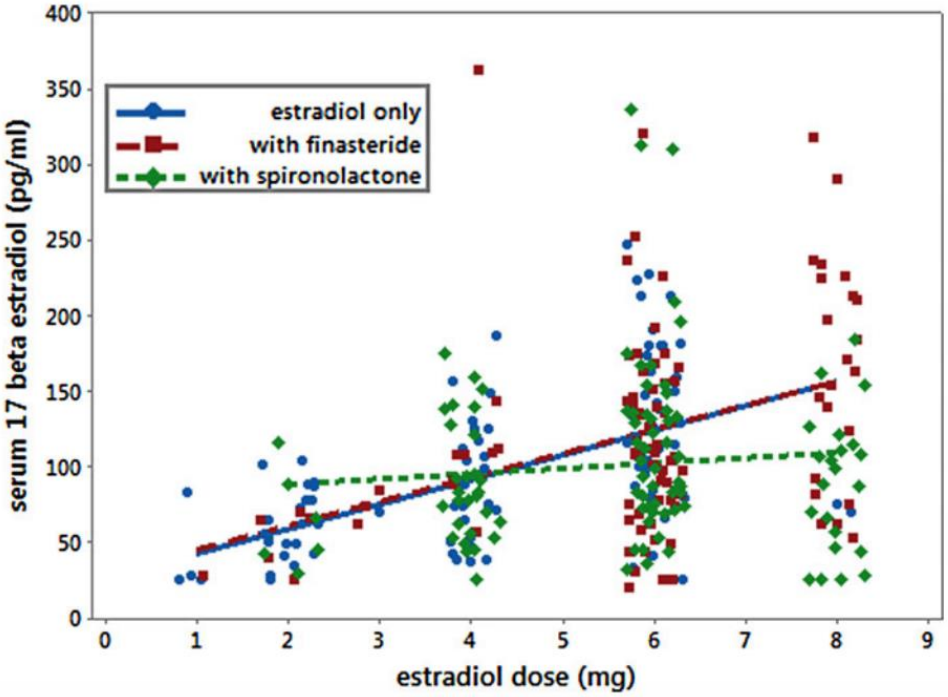
- Only 4 previous reports on bicalutamide-induced liver injury reported worldwide (as of 2016)
  - Liver function impairments were typically transient
  - Occurred within a few days or weeks of bicalutamide use
  - 2 of these patients died of fulminant hepatitis

- This is 1 case of delayed liver injury after bicalutamide therapy use — occurring 5mo after use… but levels were not checked prior (could have started earlier)
- Pt did recover

- Recommendations to monitor liver function testing regularly in the first 6mo of use, and likely continuing during entire period of use

- Leuning, et al (2018): 136 patients on 2-8mg oral estradiol alone, or in conjunction with spironolactone 100mg BID, or finasteride 5mg daily
- Spironolactone appeared to have no statistically significant impact on testosterone levels over estradiol alone
- In this study, 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.

Anti-Androgens

- None at all is an option
- Wait and start after 6 months (magic number)
- Low dose with slow up-titration

Progestins

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

  - Purported benefit on breast development, mood, sexual function
  - But cardiovascular events and breast cancer in WHI; so how does this translate to trans women?
  - Risk of weight gain? Risk of depression?

* Consider dosing 10 days each month cyclically with po form to minimize risk

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

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

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

- 290 follow-up visits of transwomen treated from January 2011 - July 2018

- Regimens include Estradiol and Spironolactone, with MPA (n = 102) or without MPA (n = 188)

- Main Outcome Measures:

. Assessed self-reported effects after MPA treatment

. Compared blood levels of E, testosterone, and other parameters w MPA vs non-MPA groups

- Results:

. E level was 210 +/- 31 pg/mL prior to MPA and 211 +/- 57 pg/mL after

. Testosterone level was 215 +/- 29 ng/dL prior to MPA use and 79 +/- 18 ng/dL after

** **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 this cohort of transwomen, they found minimal side effects, unchanged E levels, and a decline in testosterone associated with MPA

Breast Development

- **Wierckx K, Gooren L, and T'Sjoen G. (2014)Clinical review: Breast development in trans women receiving cross-sex hormones. J Sex Med 2014;11:1240–1247.**
- 11 studies, just under 1000 patients
  - Most achieved an A or B cup
  - No demonstrable effect of progestin therapy, but no evidence that progestin did NOT help
  - No negative effects of progestins
  - ?? Advantage to starting spironolactone late or to gradually increasing the dose of estradiol

"Bio-identical" Hormone Therapy

- "Bio-identical" hormone therapy
  - A compounded mixture of plant-based steroids, often administered as small implantable pellets
- These treatment are often expensive and often based on measurement and monitoring of multiple forms of estrogen and other sex hormones
- There are no studies in either cis- or transgender women that have shown these treatments to be safer or more effective than traditional allopathic hormone therapy
- Pharmacodynamics are not well studied
- Not regulated

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

Drug Interactions

Estradiol, Ethinyl Estradiol, Testosterone levels are INCREASED by:

- Nefazodone
- Fluvoxamine
- Indinavir
- Sertraline
- Diltiazem
- Cimetidine
- Itraconazole
- Fluconazole
- Clarithromycin
- Grapefruit
- Isoniazid
- Fluoxetine
- Efavirenz
- Paroxetine
- Verapamil
- Astemizole
- Ketoconazole
- Miconazole
- Erythromycin
- Triacetyloleandomycin

Drug Interactions

Estrogen levels are DECREASED by:

- Lopinavir
- Nelfinavir
- Nevirapine
- Ritonavir
- Rifampin

- **Smoking cigarettes**

- Dexamethasone
- Phenylbutazone
- Naphthoflavone
- Benzoflavone
- Sulfamide
- Sulfinpyrazone
- Phenytoin
- Carbamazepine
- Phenobarbital

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 – 5-alpha-reductase inhibitors
- Limited courses of hormone therapy

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??

Lab Monitoring

- Baseline:
  - Renal panel, if on spironolactone
  - Prolactin – for future comparison
  - Liver Enzymes, if suspicion for underlying liver disease

  - Lipids, if indicated clinically
  - Fasting Glucose, if indicated clinically
  - Testosterone level, if suspicion for hypogonadism

Ongoing Lab Monitoring

- If on spironolactone, serum electrolytes 1 to 6 weeks after start/dosage change, then every 3 months in first year, then yearly
- Serum Estradiol Levels: q 3 months with dose change
  - Ideal level is the mean daily level for premenopausal women (about 100 to 200 pg/ml)
- Serum testosterone level (at 6 to 12 months)
  - Should be less than 55 ng/dl

Case Example

- - 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

Case Example

- - 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

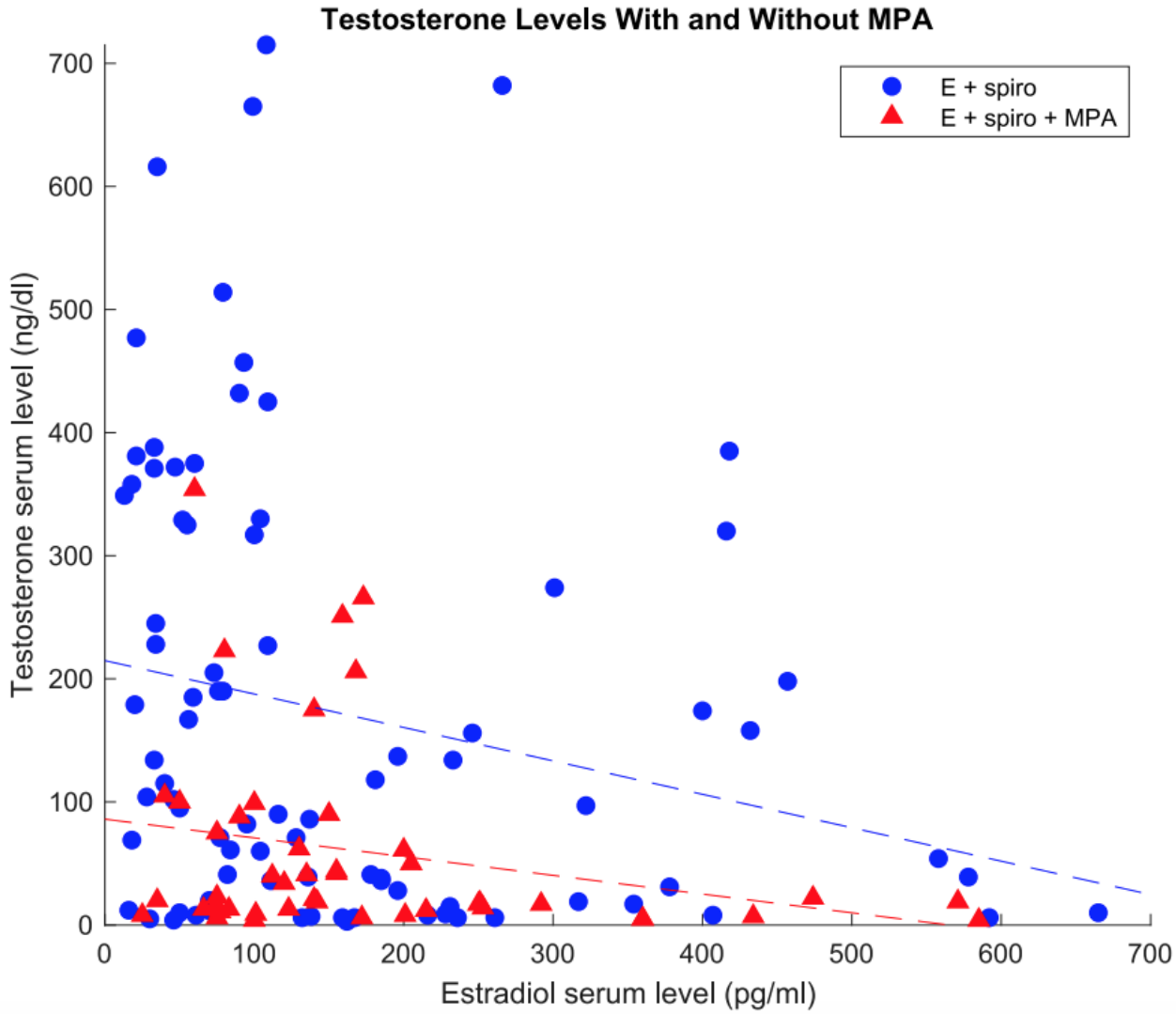

Figure 2. Total serum testosterone vs serum E in patients adhering to regimens of E and spironolactone (spiro), with or without MPA.

Case Follow Up

- **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.