# Transgender Endocrine Therapy Quick Clinical Reference Guide

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**Summary of Endocrine Society CPG (2009):**

Diagnosis:

1. Diagnosis of GID (DSM-V updated GD) made by MHP.
2. GD has high rate of remission → no endocrine intervention recommended in prepubertal children
3. Counsel regarding reversible and irreversible effects of GnRH analog and cross-hormonal therapy
4. Inform/counsel regarding fertility options prior to puberty suppression and cross-hormone treatment

Treatment of Adolescents:

1. Adolescents who fulfill readiness/eligibility criteria (diagnosis of GD by MHP, psychologically stable, living in supportive environment, increased dysphoria with puberty and have started puberty) may be treated with GnRH analogs to suppress puberty.
2. Recommend suppression of pubertal hormones start boys/girls reach T2-3 and confirm with estradiol/testosterone levels.
3. Cross-hormone treatment may be initiated if GnRH criteria above fulfilled AND are at least 16yo.
4. Recommend referring adolescent for surgery when RLE and hormonal effects had a positive effect and adolescent desires surgical intervention.
5. Surgery should be deferred until 18yo.

Hormonal Therapy:

1. Maintain cross-sex hormones in normal physiologic range of desired sex.
2. Endocrinologists should review/know onset/time course of physical changes induced by cross-sex hormone treatment.
3. Clinical/lab monitoring q3mo during first year then 1-2 times per year when on hormonal therapy.
4. Monitor PRL in MtF being treated with estrogen.
5. Evaluate CVD risk factors in patients on hormonal therapy,
6. BMD if risk factors exist and specifically for those who stop hormonal therapy once gonadectomy performed.
7. MTF who have known increased risk for BrCa should follow same breast screening recommendations for biological women.
8. MTF treated with estrogen should follow prostate screening recommended for biological men.
9. FTM should evaluate risks/benefits of hysterectomy and oophorectomy.

Surgery:

1. Surgery only considered if both MHP and endocrinologist in support.
2. Genital sex reassignment surgery recommended only after 1-year of compliant hormone therapy.
3. Endocrinologist should medically clear patient for sex reassignment surgery and collaborate with surgeon.

**Some important WPATH SOC-7 Differences:**

- RLE not required for surgery
- Age for hormonal treatment/surgery not as concrete – age of 'majority'

**DSM-V Gender Dysphoria Diagnostic Criteria:**

A. Marked incongruence between ones experienced/expressed gender and assigned gender. At least 6mo duration. Involves 2 or more:

1. Incongruence b/w expressed/experienced gender and primary/secondary sexual characteristics
2. Desire to be rid of primary/secondary sexual characteristics
3. Desire for primary/secondary characteristics of other gender
4. Desire to be of the other gender/alternative gender
4. Desire to be treated as other/alternative gender
5. Conviction that one has typical feelings of other/alternative gender

B. Clinically distressed/impaired

Subtypes: With DSD or Without DSD

**TABLE 5. Hormone therapy for adolescents**

| |
|---|
| Adolescents are *eligible* and ready for GnRH treatment if they: |
| 1. Fulfill DSM IV-TR or ICD-10 criteria for GID or transsexualism; |
| 2. Have experienced puberty to at least Tanner stage 2; |
| 3. Have (early) pubertal changes have resulted in an increase of their gender dysphoria; |
| 4. Do not suffer from psychiatric comorbidity that interferes with the diagnostic work-up or treatment; |
| 5. Have adequate psychological and social support during treatment; and |
| 6. Demonstrate knowledge and understanding of the expected outcomes of GnRH analogue treatment, cross-sex hormone treatment, and sex reassignment surgery, as well as the medical and the social risks and benefits of sex reassignment. |
| Adolescents are *eligible* for cross-sex hormone treatment if they: |
| 1. Fulfill the criteria for GnRH treatment AND |
| 2. Are 16 years or older. |
| Readiness criteria for adolescents eligible for cross-sex hormone treatment are the same as those for adults. |

Table 5. EndoSoc CPG 2009.

**Female-to-Male Hormonal Treatment** (option):

Testosterone Cypionate (Depo-Testosterone 200mg/mL)

Start 50mg IM q2wks x 6mo
Increase to 100mg IM q2wks x 6mo
Increase to 150mg IM q2wks x 6mo
Then 200mg IM q2wks (adult dose)
Transition to TDM patch when on stable dose
EndoSoc CPG: 25-50-75-100mg/$m^2$/2 weeks
*NOTE: Testosterone cypionate is suspended in cottonseed oil. Testosterone enanthate is suspended in sesame oil → allergy alert*

- Benefits
  - Permanent: growth of pubic, axillary, body hair, beard
    - Increased height (if epiphyses are not fused)
    - Accretion of bone mineral content
    - Deepening of voice, Adam's apple
    - Enlargement of clitoris (likely not to phallus size)
  - Not Permanent: increased muscle mass, male fat distro
    - Increased libido
    - Cessation of menses
- Risks
  - Permanent: Male-pattern balding
  - Not Permanent: Acne
    - Increased risk of CVD
    - Behavior changes
  - Unknown: Fertility
    - Effect on uterus, breast, ovaries
- Does NOT: Shrink breast tissue completely, male clitoris grow to the size of a penis, make uterus or ovaries regress

- Monitoring:
  - WT/BP
  - Labs:
    - Testosterone: midway between injections or anytime on patch/gel → maintain 12-24nmol/L
    - Estradiol ideally <180 pmol/L
    - CBC, CMP, lipids, fasting glucose/A1C
    - Don't forget: PAP smear, mammograms PRN, BMD

**Male-to-Female Hormonal Treatment** (option):

Estradiol Patch (Climara)

Start 25mcg patch weekly x 6mo
Increase to 50mcg weekly x 6mo
Increase to 75mcg weekly x 6mo
Then 100mcg weekly x 6mo (adult dose) – some may require up to 200mcg dose

- Benefits
  - Permanent: Breast development
    - Accretion of bone mineral content

    - Not Permanent: Soft skin
        - Decreased muscle mass
        - Female fat distro
        - Less body hair (not complete)
        - Slower balding
- Risks:
    - Permanent: ?BrCa risk
        - Decreased adult height (may actually be a benefit for MtF)
    - Not permanent: Testicular size decrease
        - Decreased libido
        - Increased TBE
    - Unknown: Fertility
        - Effect on testicles
- Does NOT: raise pitch of voice, shrink Adam's apple, shrink penis size, cause regression of beard

- Monitoring
    - WT/BP
    - Labs:
        - Estradiol keep <1600 pmol/L, ideally around 700-800 pmol/L
        - Testosterone level ideally <2 nmol/L
        - CBC, CMP, lipids, fasting glucose/A1C
        - Don't forget: BrCA, prostate screening PRN, BMD

+/- Progestins (Prometrium/Provera) – may promote breast growth or feeling of 'cycling' or Sprinolactone (anti-androgen)

Both Tables From EndoSoc CPG 2009

**TABLE 13. Masculinizing effects in FTM transsexual persons**

| EFFECT | ONSET[a] (months) | MAXIMUM[a] (years) |
|---|---|---|
| Skin oiliness/acne | 1 – 6 | 1 – 2 |
| Facial/body hair growth | 6 – 12 | 4 – 5 |
| Scalp hair loss | 6 – 12 | b |
| Increased muscle mass/strength | 6 – 12 | 2 – 5 |
| Fat redistribution | 1 – 6 | 2 – 5 |
| Cessation of menses | 2 – 6 | c |
| Clitoral enlargement | 3 – 6 | 1 – 2 |
| Vaginal atrophy | 3 – 6 | 1 – 2 |
| Deepening of voice | 6 – 12 | 1 – 2 |

a *Estimates represent clinical observations. See Refs 81, 92, 93.*
b *Prevention and treatment as recommended for biological men.*
c *Menorrhagia requires diagnosis and treatment by a gynecologist.*

**TABLE 14. Feminizing effects in MTF transsexual persons**

| EFFECT | ONSET[a] | MAXIMUM[a] |
|---|---|---|
| Redistribution of body fat | 3 – 6 months | 2 – 3 years |
| Decrease in muscle mass and strength | 3 – 6 months | 1 – 2 years |
| Softening of skin/decreased oiliness | 3 – 6 months | Unknown |
| Decreased libido | 1 – 3 months | 3 – 6 months |
| Decreased spontaneous erections | 1 – 3 months | 3 – 6 months |
| Male sexual dysfunction | Variable | Variable |
| Breast growth | 3 – 6 months | 2 – 3 years |
| Decreased testicular volume | 3 – 6 months | 2 – 3 years |
| Decreased sperm production | Unknown | > 3 years |
| Decreased terminal hair growth | 6 – 12 months | > 3 years[b] |
| Scalp hair | No regrowth | c |
| Voice changes | None | d |

*a Estimates represent clinical observations. See Refs 81, 92, 93.*
*b Complete removal of male sexual hair requires electrolysis or laser treatment or both.*
*c Familial scalp hair loss may occur if estrogens are stopped.*
*d Treatment by speech pathologists for voice training is most effective.*

Resources:

- www.wpath.org – SOC-7 (2012)
- Endocrine Society Guidelines (2009)
- UCSF - http://transhealth.ucsf.edu
- raisingmyrainbow.com
- transparenthood.net
- TRANSLINE
- www.glaad.org
- transyouthequality.org
- U. Maryland Pediatric Endocrinology (Dr. Pine)
- Whitman-Walker Health - whitman-walkter.org

# Risks of Feminizing Hormone Therapy (MtF)

**Likely Increased Risk:**

Venous thromboembolic disease

- Estrogen use increases the risk of venous thromboembolic events (VTE), particularly in patients who are over age 40, smokers, highly sedentary, obese, and who have underlying thrombophilic disorders.
- This risk is increased with the additional use of third generation progestins.
- This risk is decreased with use of the transdermal (versus oral) route of estradiol administration, which is recommended for patients at higher risk of VTE.

Cardiovascular, cerebrovascular disease

- Estrogen use increases the risk of cardiovascular events in patients over age 50 with underlying cardiovascular risk factors. Additional progestin use may increase this risk.

Lipids

- Oral estrogen use may markedly increase triglycerides in patients, increasing the risk of pancreatitis and cardiovascular events.
- Different routes of administration will have different metabolic effects on levels of HDL cholesterol, LDL cholesterol and lipoprotein(a).
- In general, clinical evidence suggests that MtF patients with pre-existing lipid disorders may benefit from the use of transdermal rather than oral estrogen.

Liver/gallbladder

- Estrogen and cyproterone acetate use may be associated with transient liver enzyme elevations and, rarely, clinical hepatotoxicity.
- Estrogen use increases the risk of cholelithiasis (gall stones) and subsequent cholecystectomy.

**Possible Increased Risk:**

Type 2 diabetes mellitus

- Feminizing hormone therapy, particularly estrogen, may increase the risk of type 2 diabetes, particularly among patients with a family history of diabetes or other risk factors for this disease.

Hypertension

- Estrogen use may increase blood pressure, but the effect on incidence of overt hypertension is unknown.
- Spironolactone reduces blood pressure and is recommended for at-risk or hypertensive patients desiring feminization.

Prolactinoma

- Estrogen use increases the risk of hyperprolactinemia among MtF patients in the first year of treatment, but this risk is unlikely thereafter.
- High-dose estrogen use may promote the clinical appearance of preexisting but clinically unapparent prolactinoma.

**Inconclusive or No Increased Risk:**

Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

Breast cancer

- MtF persons who have taken feminizing hormones do experience breast cancer, but it is unknown how their degree of risk compares to that of persons born with female genitalia.
- Longer duration of feminizing hormone exposure (i.e., number of years taking estrogen preparations), family history of breast cancer, obesity (BMI >35), and the use of progestins likely influence the level of risk.

**Other Side Effects of Feminizing Therapy:**

The following effects may be considered minor or even desired, depending on the patient, but are clearly associated with feminizing hormone therapy.

Fertility and sexual function

- Feminizing hormone therapy may impair fertility.
- Feminizing hormone therapy may decrease libido.
- Feminizing hormone therapy reduces nocturnal erections, with variable impact on sexually stimulated erections.

**Risks of Anti-Androgen Medications:**

Feminizing hormone regimens often include a variety of agents that affect testosterone production or action. These include GnRH agonists, progestins (including cyproterone acetate), spironolactone, and 5-alpha reductase inhibitors. An extensive discussion of the specific risks of these agents is beyond the scope of the *SOC*. However, both spironolactone and cyproterone acetate are widely used and deserve some comment.

Cyproterone acetate is a progestational compound with anti-androgenic properties (Gooren, 2005; Levy et al., 2003). Although widely used in Europe, it is not approved for use in the United States because of concerns about hepatotoxicity (Thole, Manso, Salgueiro, Revuelta, & Hidalgo, 2004). Spironolactone is commonly used as an anti-androgen in feminizing hormone therapy, particularly in regions where cyproterone is not approved for use (Dahl et al., 2006; Moore et al., 2003; Tangpricha et al., 2003). Spironolactone has a long history of use in treating hypertension and congestive heart failure. Its common side effects include hyperkalemia, dizziness, and gastrointestinal symptoms (*Physicians' Desk Reference*, 2007).

# Risks of Masculinizing Hormone Therapy (FtM)

**Likely Increased Risk:**

Polycythemia

- Masculinizing hormone therapy involving testosterone or other androgenic steroids increases the risk of polycythemia (hematocrit > 50%), particularly in patients with other risk factors.
- Transdermal administration and adaptation of dosage may reduce this risk.

Weight gain/visceral fat

- Masculinizing hormone therapy can result in modest weight gain, with an increase in visceral fat.

**Possible Increased Risk:**

Lipids

- Testosterone therapy decreases HDL, but variably affects LDL and triglycerides.
- Supraphysiologic (beyond normal male range) serum levels of testosterone, often found with extended intramuscular dosing, may worsen lipid profiles, whereas transdermal administration appears to be more lipid neutral.
- Patients with underlying polycystic ovarian syndrome or dyslipidemia may be at increased risk of worsening dyslipidemia with testosterone therapy.

Liver

- Transient elevations in liver enzymes may occur with testosterone therapy.
- Hepatic dysfunction and malignancies have been noted with oral methyltestosterone. However, methyltestosterone is no longer available in most countries and should no longer be used.

### Psychiatric

Masculinizing therapy involving testosterone or other androgenic steroids may increase the risk of hypomanic, manic, or psychotic symptoms in patients with underlying psychiatric disorders that include such symptoms. This adverse event appears to be associated with higher doses or supraphysiologic blood levels of testosterone.

**Inconclusive or No Increased Risk:**

Items in this category include those that may present risk, but for which the evidence is so minimal that no clear conclusion can be reached.

### Osteoporosis

- Testosterone therapy maintains or increases bone mineral density among FtM patients prior to oophorectomy, at least in the first three years of treatment.
- There is an increased risk of bone density loss after oophorectomy, particularly if testosterone therapy is interrupted or insufficient. This includes patients utilizing solely oral testosterone.

### Cardiovascular

- Masculinizing hormone therapy at normal physiologic doses does not appear to increase the risk of cardiovascular events among healthy patients.
- Masculinizing hormone therapy may increase the risk of cardiovascular disease in patients with underlying risks factors.

### Hypertension

- Masculinizing hormone therapy at normal physiologic doses may increase blood pressure but does not appear to increase the risk of hypertension.
- Patients with risk factors for hypertension, such as weight gain, family history, or polycystic ovarian syndrome, may be at increased risk.