Adverse Outcome Prevention and Long-Term Care

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Outclinic patients for Endocrinology

and Metabolic Diseases

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Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Bayer

Introduction

- In transgender subjects, the Hormonal Replacement Therapy (HRT) may provide the same risks during HRT which may occur in hypogonadal subjects.
- The risks can rise whenever you use supraphysiological or inadequate substitutive doses for those subjects.
- Accurate clinical history should be took as means of knowing possible clinical conditions that require a preventive therapy (e.g. familiarity for breast cancer or thrombophilia, liver diseases, etc).

Clinical conditions that can be worsened by HRT in transmen

- higher risk: for uterine and breast cancer:
  for erythrocytosis;

They need to be treated before starting HRT

- Moderate risk for liver diseases (hypertransaminasemia > 3 times above normal serum limit)

Hembree et al. J Clin End Metab, 2009;9:3132-3154

Clinical conditions that can be worsened by HRT in transwomen

- Higher risk for important adverse effects (thromboembolic disease)

- Moderate risk for: breast cancer;
  liver diseases (Hypertransinasemia >3 times)
  hyperprolactinemia
  cardiovascular diseases
  severe headache

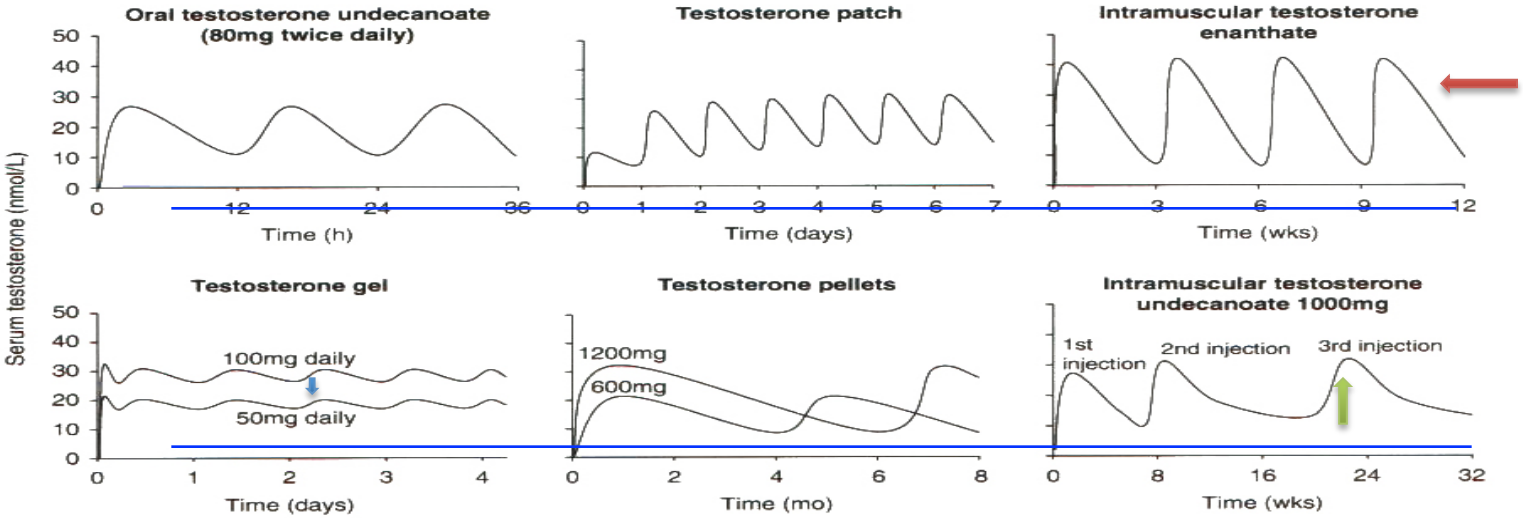
They need to be treated before starting HRT

Hembree et al. J Clin End Metab, 2009;9:3132-3154

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:[a]
   a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
   b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
   c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

Serum T in different forms of T application



L J.G.Gooren and M.C.M. Bunck Drugs 64,2004

TRT in transmen: serum lipids levels and CV risk

Meta-analysis from 16 studies

Clinical Endocrinology (2010) 72, 1–10 doi: 10.1111/j.1365-2265.2009.03632.x

REVIEW ARTICLE

Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses

Mohamed B. Elamin*, Magaly Zumaeta Garcia*, Mohammad Hassan Murad*,†, Patricia J. Erwin*,‡ and Victor M. Montori*,§

*Knowledge and Encounter Research Unit, †Division of Preventive Medicine, ‡Mayo Clinic Libraries and §Division of Endocrinology, Diabetes, Metabolism, Nutrition, Mayo Clinic, Rochester, MN, USA

TRT (in different formulation) in FtM caused an atherogenic profile:

-↓ HDL

-↑ TgI

- PA ↑ 1.74 mmHg

TRT and CV risk in transmen

European Journal of Endocrinology (2009) **161** 795–798 ISSN 0804-4643

CLINICAL STUDY

Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals

J W Jacobeit, L J Gooren[1] and H M Schulte

T UNDECANOATO i.m. administered for 36 mm. in FtM caused:

- ↓ HDL but not significant (p=0.34)
- = TgI
- ↓ colest tot (p=0.004)

TRT and CV risk: insulin-resistance

Results mixed :

-↑IR :13 FtM, T ester 250 mg/2 weeks
(Polderman KH, J Clin End Metab 1994;79:265.271)

-Not ↑IR :17 FtM, T ester 250 mg/2 weeks
(Elbers et al. Clin End 2003, 58:562-571)
15 FtM with Nebid 1000
(Meriggiola MC, J Sex Med 2008 5:2442-2453; Resmini E, J of Andr 2008,29:580-585)

TRT in transmen: adipose tissue and muscle mass

-↑ ***body weight*** *(+2.7 kg)*

- ↑ ***abdominal adipose tissue (+13%)***
- ↓ ***subcutaneous adipose tissue (-22%)***

(Elbers JM Clin Endoc 2003;58:562-571)

TRT in transmen: BMD

- ✓ Evaluate the BMD taking into consideration the presence of possible risk factors for osteoporosis (ie chronic F therapy) or above all when one stops TRT after gonadectomy.
- ✓ serum LH could serve as a parameter of appropriate doses of TRT to prevent BMD
- ✓ No definitive data on fracture are available

(Hembree et al. J Clin End Metab 2009;94:3132-3154
Gooren & Giltay J Sex Med 2008;5:765;776)

TRT in transmen: erythrocytosis

- ✓ >Hct 2-5 times compared with baseline value in 46,XY Hypogonadal; 6-25% developed erythrocytosis (Hct >50%)
  (Drinka PJ J Am Soc 1995;43:899-901; Kaufman JM & Vermeulen A End Review 2005;26:833.876)

- ✓ There is polycithemia in some transmen, although there are no systematic studies
  (Jacobeut JW, Gooren LJ, Shulte HM Eur J End 2009;161-795-798)

TRT complication in transmen: endometrial cancer

✓**<u>IN MENOPAUSAL WOMEN</u>**: **adding T and E ↓ cause endometrial hyperplasia** (Gelfand MM,.Prog Clin Biol Res 1989;320:29–40. Hickok LR,Obstet Gynecol 1993;82:919–24.Zang H, J Clin Endocrinol Metab 2007;92:2169–75.)

✓Conflicting data

-Endometrial hyperplasia in transmen treated with TRT (T aromatization into E?)(Futterweit W, Arch Sex Behav 1998. 27:209-226)

- Endometrial atrophy in transmen treated with TRT

Miller N Histopatology 1986,10:661-69;Perrone AM,J Sex Med. 2009 Nov;6(11): 3193-200. Epub 2009 Jun 29;Grymberg M, Reprod Biomed Online. 2010;20:553-558.

-NO CASES OF ENDOMETRIAL CANCER HAVE BEEN REPORTED SO FAR

TRT complication in transmen
Ovary cancer

✓**TRT lasting more than 18 months could upregulate AR (risk factor for OC)** (Chandha S, Hum Path 1994;25:1198-1204)

✓ **TRT can cause PCOS-like ovarian characteristics** (Spinder T,Cl End and Metab1989;69:151–157.Grymberg M, Reprod Biomed Online. 2010;20:553-558.)

✓**3 cases of OC have been reported** (Dizon DS, Gynec Obstet Invest 2006;62:226-228; Hage JJ, Gynecol Oncol. 2000;76(3):413-5.

TRT in transmen: endometrial and ovary cancer?

Since performing gynecological instrumental examinations is a discomfort to transmen, it is recommended to perform istero-annessiectomy to prevent the risk of reproductive tract K (within 18-24 months)

Hembre et al. J Clin End Metab 2017

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
   a. Serum testosterone levels should be <50 ng/dL.
   b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

Estrogen Replacement Therapy in transwomen: thromboembolic risk

- ↑ 20 times in transfemales in cross sex tp (van Kesteren et al,Cl End 1997;47:337-42)

- ++ with EE (in 2-6%); < risk with transdermal E (Toorians et al J Clin End Metab 2003:88:5723-39)

1. TVE is a rare event during ETR cross-sex
2. Trombophilia screening should be restricted to trangender person with history of familiar TVE
3. ETR can be used in transfemale

(Ott J et al. Fertil Steril. 2010 Mar 1;93:1267-72.)

ETR in transwomen: hyperPRL

- Up to 20% of transfemale treated with ETR may have hyperPRL and/or enlargement of pituitary gland.
- Clinicians should measure PRL levels at baseline and at least yearly for the first 2 years of therapy, especially in those subjects receiving psychotropic drugs.
- Transfemale with hyperPRL after ERT whitdrawal can undergo MNR.

ETR in transwomen: CV risk

- ↑ **HDL (+16%)**
- ↓ **LDL (-12%)**

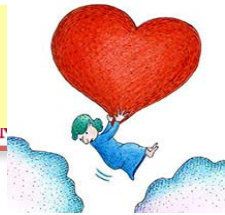
(Elbers et al Clin End 2003;58:562-571)

but neutralized by

- ↑ **weight, BMI (+6%),**
- ↑ **visceral fat (+18%)**
- ↑ **PA**
- ↑ **IR**

(Hembree et al et al Clin End 2009;94:3132-3154)
(Gooren et al J Clin End 2008,93:19-25)

ERT in transwomen: CV risk



In 10 yrs follow-up, there was no increase in CV mortality

Van kesteren et al PJ Clin End 1997;47:337-342

ERT in transwomen: CV risk

Meta-analysis of 16 studies

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Limited and unconvincing evidence

Elamin MB et al, Clin End 2009;

ERT in transwomen: BMD

In adult men, E2 levels correlate significantly better with BMD than serum T (Amin et al Ann Int Med 2000;133:951-963)

E therapy prevents BMD loss in transfemale.

(van kesteren P et al Cl end 1998:347-54. Mueller A et al Eur J End 2005,153:2266-2274. Ruetsche AG et al Osteoporos Int 2005,16:791-98)

Fracture data are not available

Hembee et al JCEM, 2017

ERT in transwomen: prostate cancer

- **Rare < 40 yrs++ in androgenic deprivation therapy** (Smith RA et al 2006 CA Cancer J Cl 56:11-25)

- **E does not cause BPH or modification of premalignant lesions** (van kesteren et al J Urol 1996:156:1349-1353)

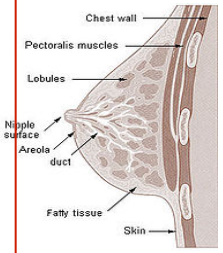
- **3 reported cases of prostate cancer, but in pts who received hormonal therapy when > 50 aa** (Sulser et al. Urol Int 2005;75:288-290, Dorff RB et al Clin Genitourin Cancer 2007,5:355-346. Thurston Br J Urol 1994:73:217)

ERT in transwomen: Prostate cancer

Even though it is a discomfort in transfemale: when starting ERT > 20 years, screening PSA and rectal esploration yearly according to guidelines U.S. Preventive Serivice Task Force

(Hembree et al J End Inv 2009,94:3132-54; Hembree et al JCEM, 2017)

ERT in transwomen: breast cancer

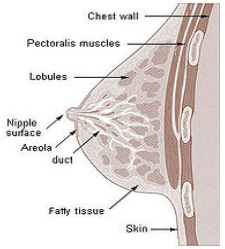


- **46,XX treated with conjugated E without P for 7 yrs: no ↑ risk** (Andreson et al, Women's Health Initiative randomized controlled trial. JAMA 291:1701-12)

- **45,XO on ERT: ↓** risk ***vs*** **normal women** (Bosde P N Engl J med 2006,355:2599-2600. Schoemaker MJ et al, Lancet Oncol 2008,9:239-46)

In a Dutch Cohort made up of 1800 participants: only 1 case of breast cancer reported during 15 yrs (Hembree et al JCEM, 2009)

ERT in transwomen: breast cancer



- **In medium and long term studies in transfemales there is no increased risk during ERT.**
- **Follow-up for breast cancer according to international guidelines** (Hembree et al JCEM, 2009, 2017)

Cross-sex hormones and fertility

-After when?
-Is it reversible?
-Crioconservation of the gametes before starting hormone therapy?

-In Italy after the change of register (Act No. 164/1982, Sexual Alteration Rules) complicated withdraw cryopreserved.

(Godano A et al J End Invest 2009,32:857-864)

Surgery for sex-reassignment and gender confirmation

- Types of surgery that do not affect fertility: eg mastectomy (transmen) or breast enlargement (transwomen).
- Types of surgery that affect fertility (irreversibile techniques): eg gonadectomy; external genital removal (eg penectomy) and reconstruction (eg neovagina).

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (*e.g.*, cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

Conclusions

- In transgender subjects the hormonal replacement therapy should be conducted according to guidelines for hypogonadal subjects, including their side effects.
- The patient must actively participate in medical choices and in particular his/her satisfaction must drive the work of physician.
- Surgery for sex reassignment should never be started if one does not find a clear physical and mental satisfaction in the new desired sex condition, also in function of fertility preservation.

Gerda Ewegener

Danish art Museum ARKEN

Many thanks to all of us