NHS Gender Identity Clinic
Charing Cross Hospital

# Transgender medicine – the endocrine aspects

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# Incidence of Transsexualism

- 1:30,000 natal males. 1:100,000 natal females seek SRS. (APA, 2000)
- 1:7440 for natal males 1:31,153 for natal females. (Wilson, Sharp and Carr, 1999)
- A non-conservative estimate is that 8-10% of the United States population has some degree of GD. (Ettner,1999)
- 5% of population seeking trans related services (NHS Calderdale, 2009)

# Gender Identity Disorder

- DSM-IV

  Strong and persistent cross-gender identification and a persistent discomfort with their sex or a a sense of inappropriateness in the gender role of that sex

# ICD-10 Transsexualism

- The desire to live and be accepted as a member of the opposite sex usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatment
- The transgender identity has been present for a minimum of 2 years
- The disorder is not a symptom of another mental disorder or chromosomal disorder

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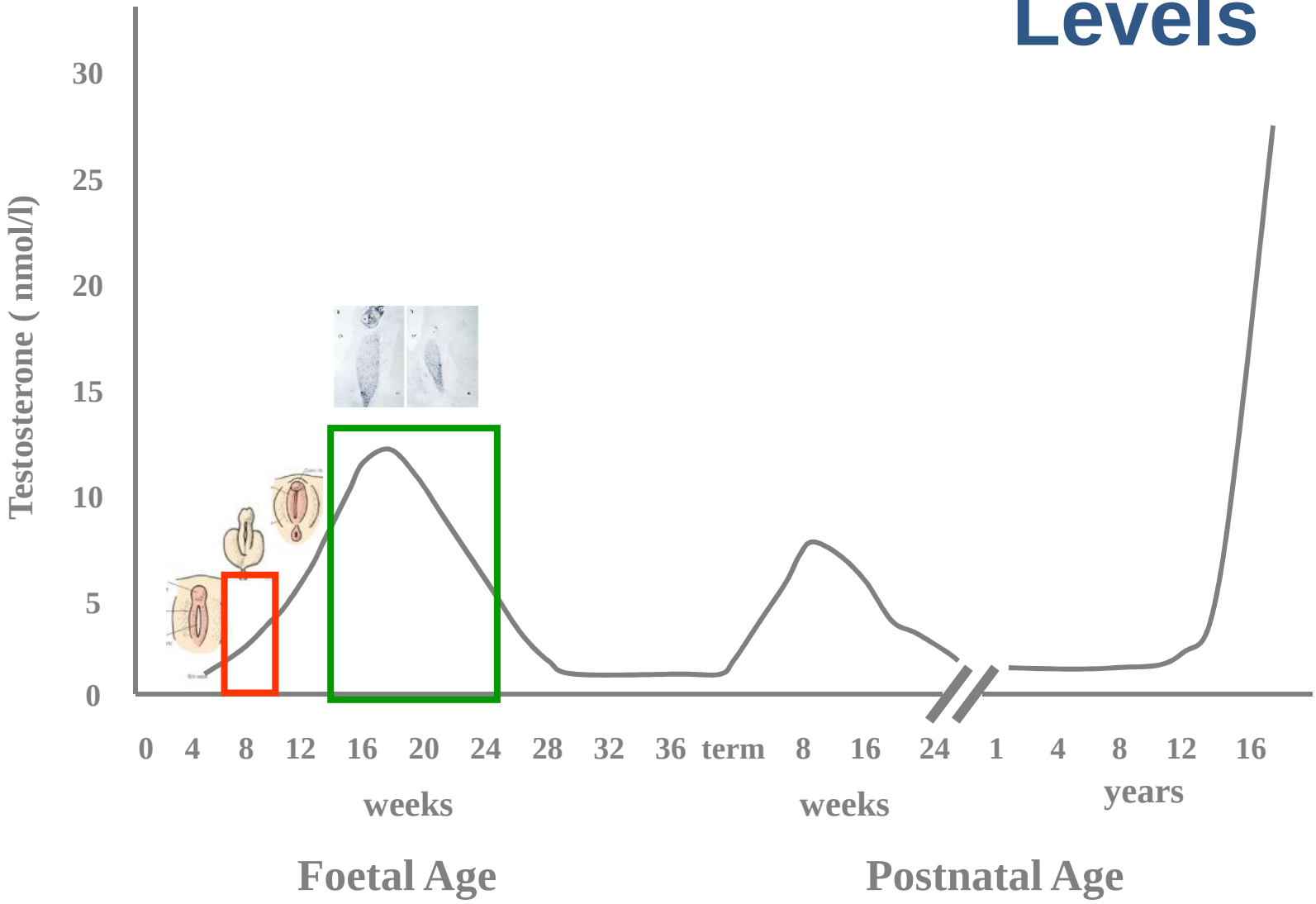
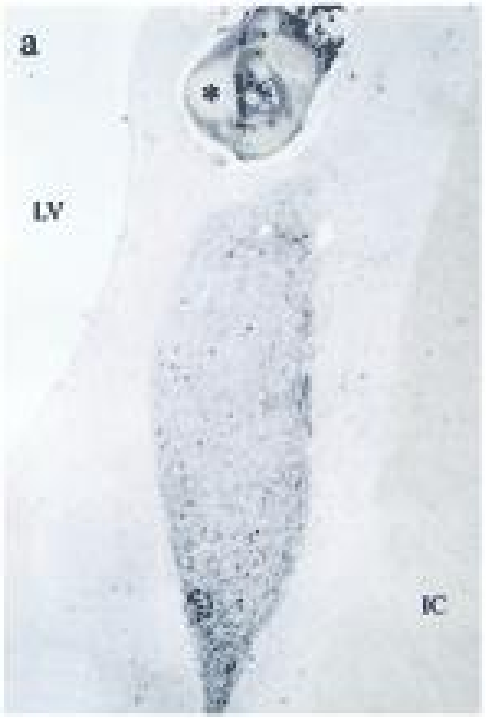
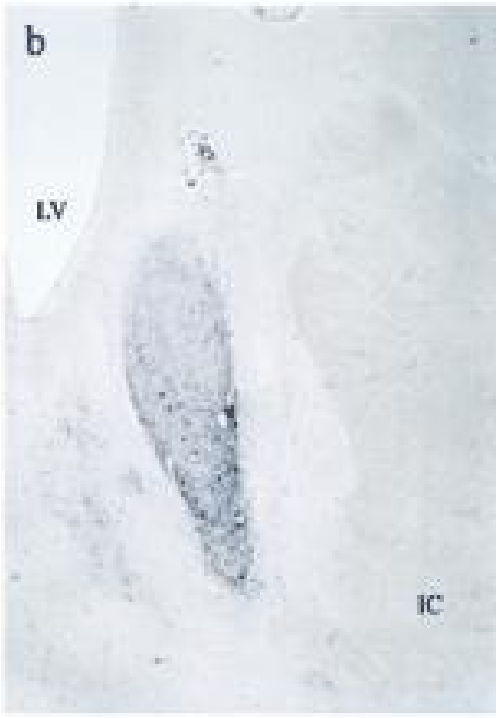
# Plasma Testosterone Levels



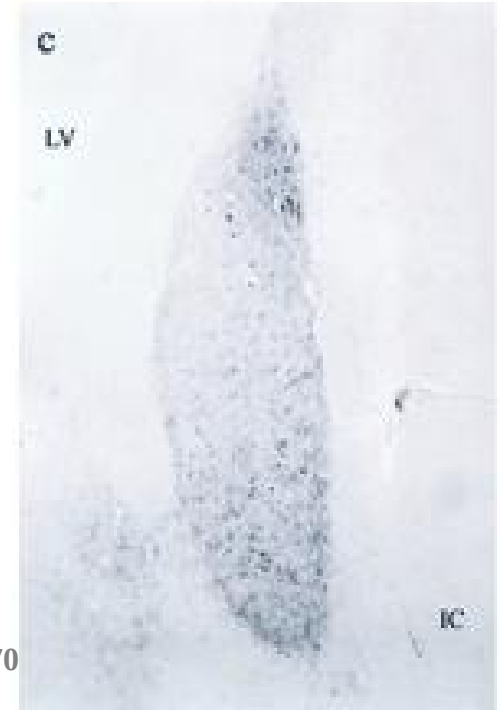
heterosexual male

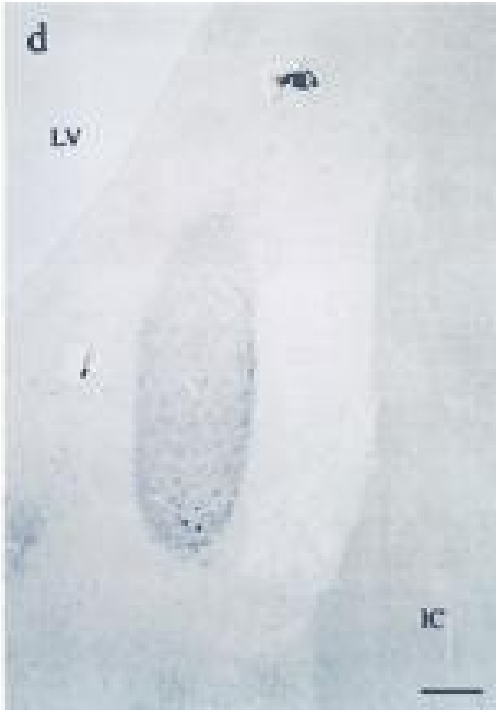



heterosexual female

homosexual male




mtf transsexual

Zhou 1995 Nature 378 68-70

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# Role of Endocrinologist in the Management of Gender Dysphoria

- Diagnosis of associated endocrine abnormalities
- Hormonal treatment of transgender patients

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# Role of Endocrinologist in the Management of Gender Dysphoria

- Diagnosis of associated endocrine abnormalities

- Hormonal treatment of transgender patients

# Associated Conditions

- Intersex
  - Congenital adrenal hyperplasia
  - Androgen insensitivity
  - Gonadal dysgenesis
  - 5α reductase deficiency
  - Aromatase deficiency
- Chromosomal abnormality
  - Kleinfelter's syndrome
  - Turner's Syndrome
- Exogenous Hormone exposure

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# Monitoring Initial Visit

| | |
|---|---|
| LH | Weight |
| FSH | Blood Pressure |
| Testosterone | Lipid profile |
| Oestradiol | Glucose |
| SHBG | |
| Prolactin | |
| Dihydrotestosterone | |

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# Role of Endocrinologist in the Management of Gender Dysphoria

- Diagnosis of associated endocrine abnormalities

- Hormonal treatment of transgender patients

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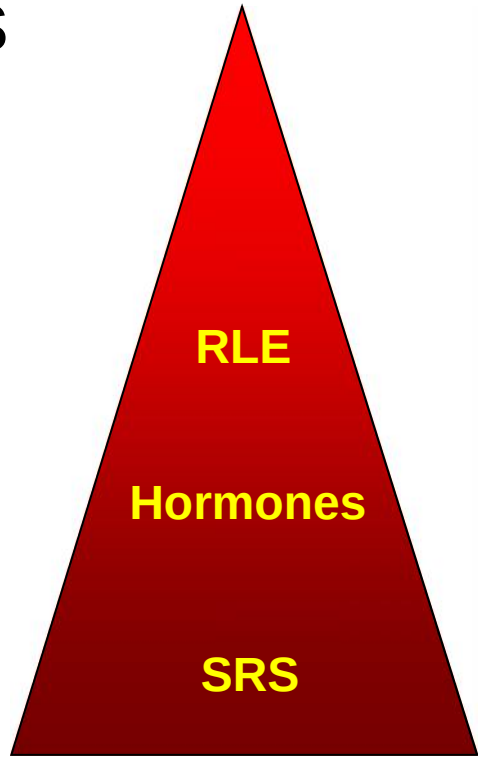
# Tridadic Therapy

- The principal of treatment is Tridadic Therapy

- Real Life Experience
- Hormonal Therapy of the Desired Gender
- Sex Reassignment Surgery



# Aim of therapy

- To Suppress genetic sex hormone production
- Induce sexual development of desired gender
- Prevent long term complications of hypogonadism

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# Criteria for hormone therapy

- Initiation of hormone therapy may be undertaken after a psychosocial assessment has been conducted and informed consent has been obtained by a qualified health professional
- 1. Persistent, well-documented 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.

# Diagnosis

- Adult Specialist
- Mental health professional with appropriate qualification in that field
- Specialised training in the diagnosis of DSM/IDC-10 Sexual Disorders
- Training in psychotherapy
- CPD in gender disorders

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# Hormone Regimens Used

| Center | Feminizing hormone regimens | Masculinizing hormone regimes | N |
|---|---|---|---|
| Academic Hospital Vrije Universiteit, Amsterdam, Netherlands (5–7) | Ethinyl estradiol 100 μg/d or transdermal 17β-estradiol 100 μg/twice a week and cyproterone acetate 100 mg/d | Testosterone esters 250 mg im every 2 wks or testosterone undecanoate 160 mg/d | 816 M→F<br>293 F→M |
| Psychoneuroendocrinology Unit, University of Liège, Liège, Belgium (8) | Ethinyl estradiol 50–100 μg/d, conjugated equine estrogens 1.25–2.50 mg/d, or estradiol benzoate 25 mg/wk<br>Optional, spironolactone 100–200 mg/d or cyproterone acetate 50–100 mg/d | Testosterone 240 mg/d in three doses or testosterone esters 250 mg im every 2–4 wk | Unreported |
| Division of Endocrinology, Mount Sinai School of Medicine, New York, NY (9, 10) | Ethinyl estradiol 100 μg/d or conjugated equine estrogens 1.25–2.5 mg/d and medroxyprogesterone acetate 5–10 mg/d for 10 d/month during the first 6 months<br>Optional, spironolactone 100–200 mg/d or cyproterone acetate | Testosterone esters (cypionate or enanthate) 250–400 mg im every 2–3 wk | 93 F→M |
| Department of Endocrinology, University of British Columbia, Vancouver, British Columbia, Canada (11) | Conjugated equine estrogen 0.625 g/d increased to 5 g/d for 3 of 4 wk and spironolactone 100–200 mg/d gradually increased until testosterone suppression; and medroxyprogesterone 10 mg/d 2 wk/month or continuously if needed | Unreported | 50 M→F |
| Max-Planck-Institute Endocrinological Clinic, Munich, Germany (12, 13) | Estradiol 80–100 mg im every 2 wks, then 17β-estradiol 2–8 mg/d after 1 yr and cyproterone acetate 100 mg/d for 6–12 months until testosterone is lowered | Testosterone esters 250 mg im every 2 wk, reduce in 9–12 months after desired effects to every 2–4 wk<br>Optional, progesterone 500 mg im two doses 3–4 d apart between testosterone doses | 129 total |
| Gender Clinic, University of Texas Medical Branch, Galveston, Texas (14, 15) | Ethinyl estradiol 100 μg/d or conjugated equine estrogens 7.5–10 mg/d | Testosterone cypionate 200 mg im every 2 wk | 60 M→F<br>30 F→M |
| Department of Obstetrics and Gynecology, National University of Singapore, Singapore (16) | Unreported | Testosterone esters 250 mg im every 3–4 wk or testosterone cyclopentylpropionate 100 mg im every week | 70 F→M |

All doses are oral unless otherwise noted

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# *Standard preoperative treatment protocol at Charing Cross Hospital Gender Identity Clinic*

- Oestrogen Valerate 2-10mg/day
- Decapeptyl 11.25mg/12wk

***or***

- Transdermal
  - Oestrogen Valerate Gel (Sandrena)1-4mg/day
  - Patches (50-200mgx2/week)

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# Oestrogen Effects in Transwomen

| EFFECT | ONSET | MAXIMUM |
|---|---|---|
| Redistribution of body fat months | 3 – 6 | 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 |
| Scalp hair | No regrowth | |
| Voice changes | None | |

Hembree JCEM 2009, 94(9):3132–3154

# Hormone Replacement

- Maximum effect takes up to 2 years Transwomen 5 years Transmen
- Increasing doses does not lead to increasing effect
- Response is individual
- Genetic make up limits the tissue response

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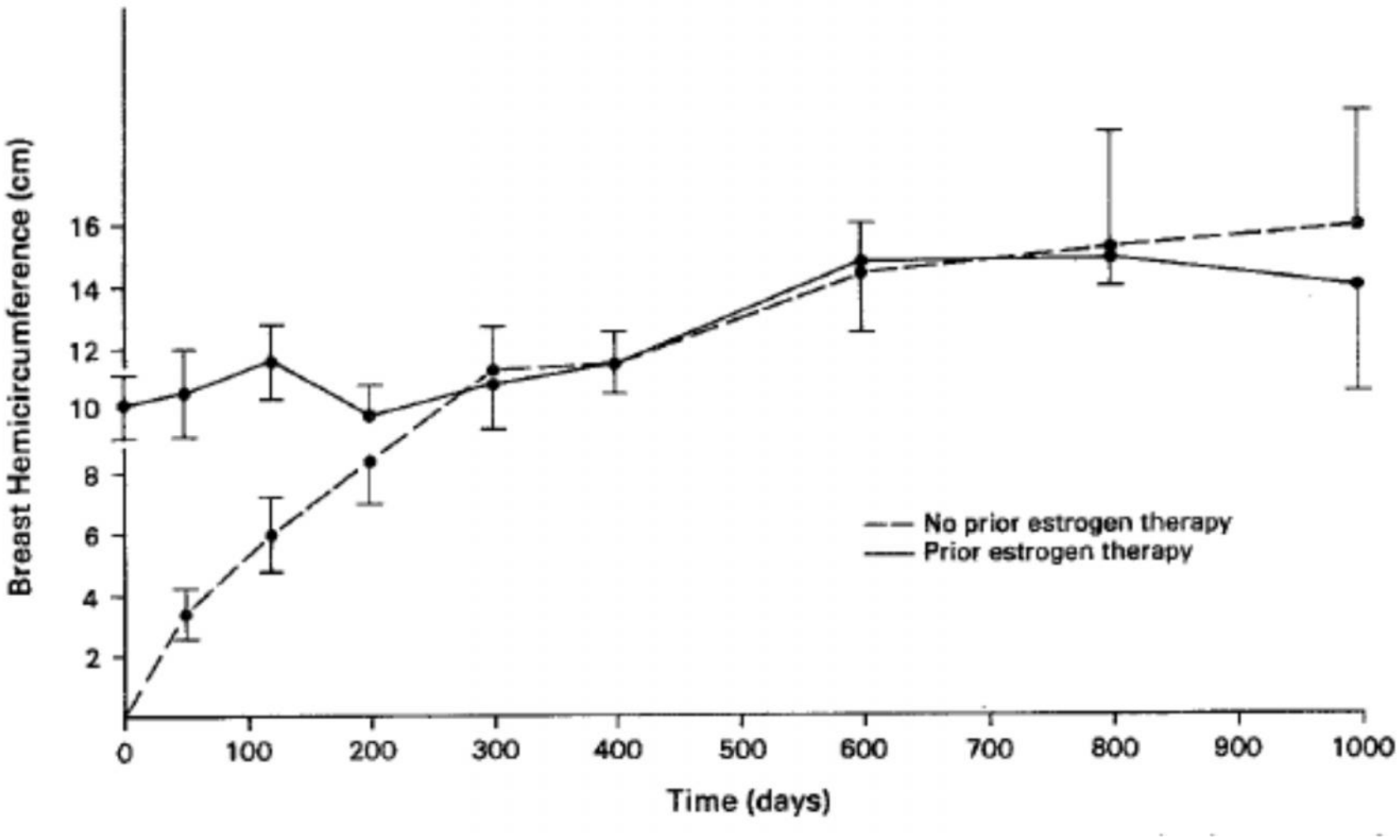
# Time Course of Breast Development in Transwomen




Mayer III 1986 Arch of Sex Behav 15 (2) 121-138

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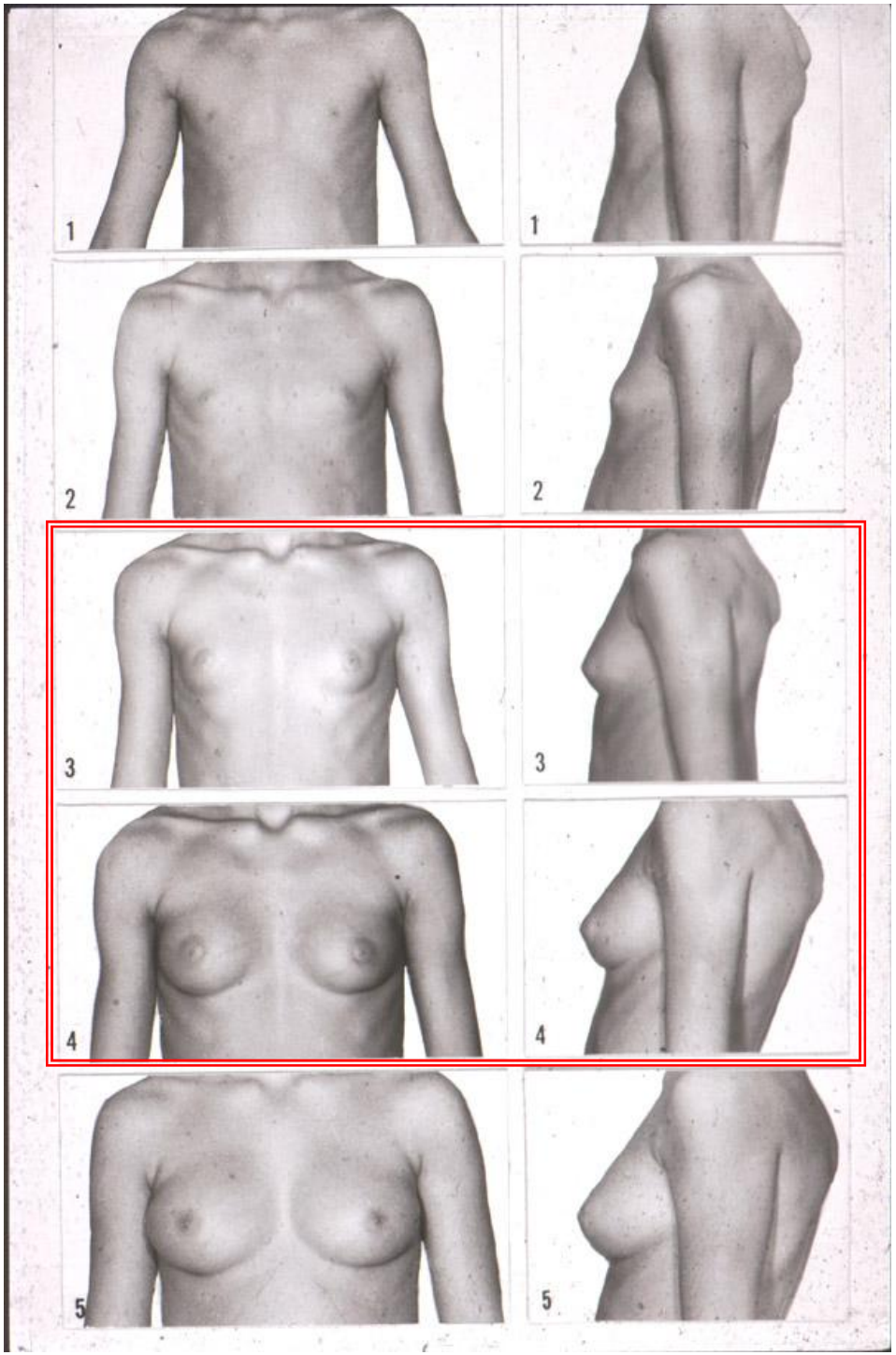

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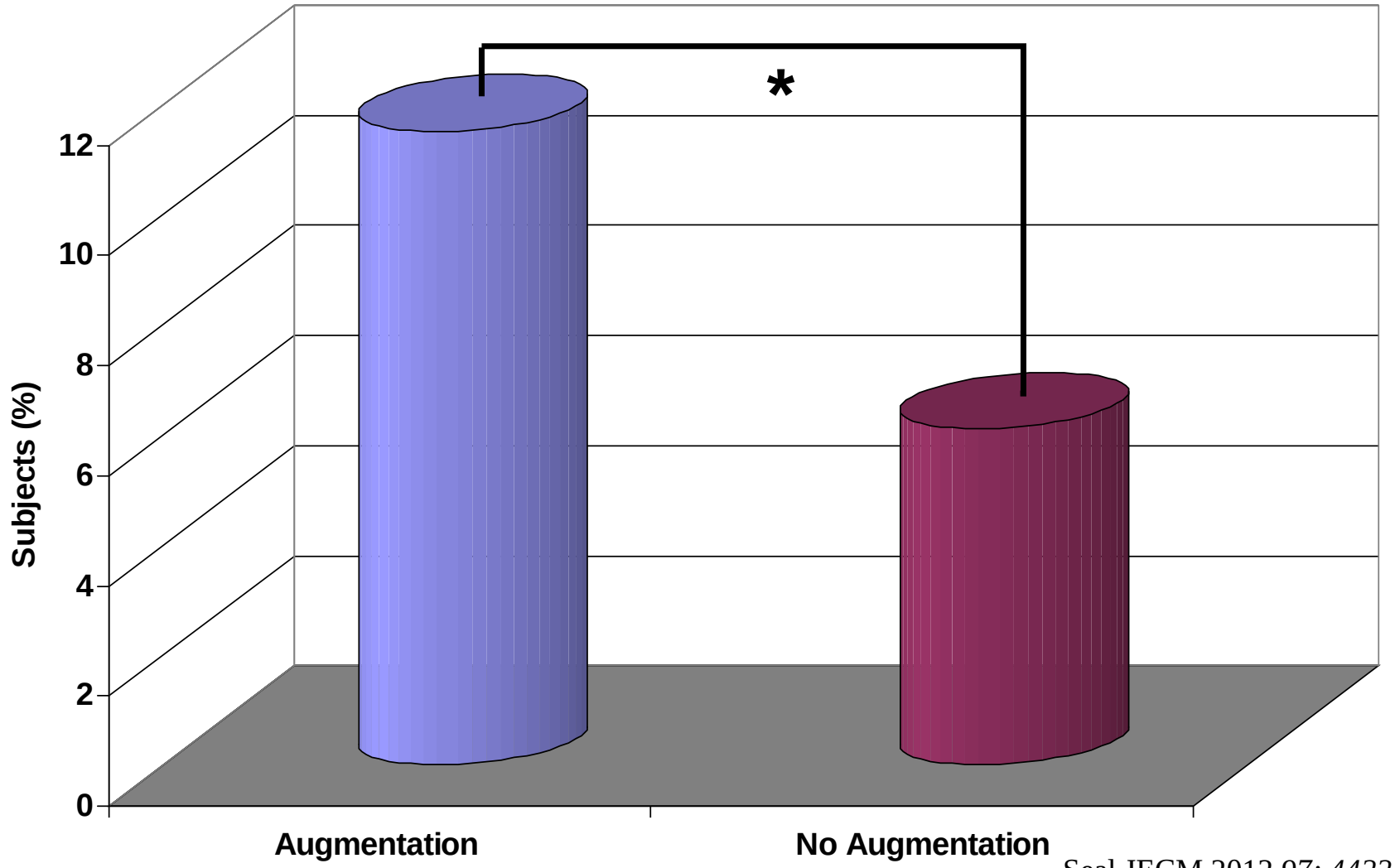
# Need for Augmentation by Self-medication Status




Seal JECM 2012 *97: 4422-4428*

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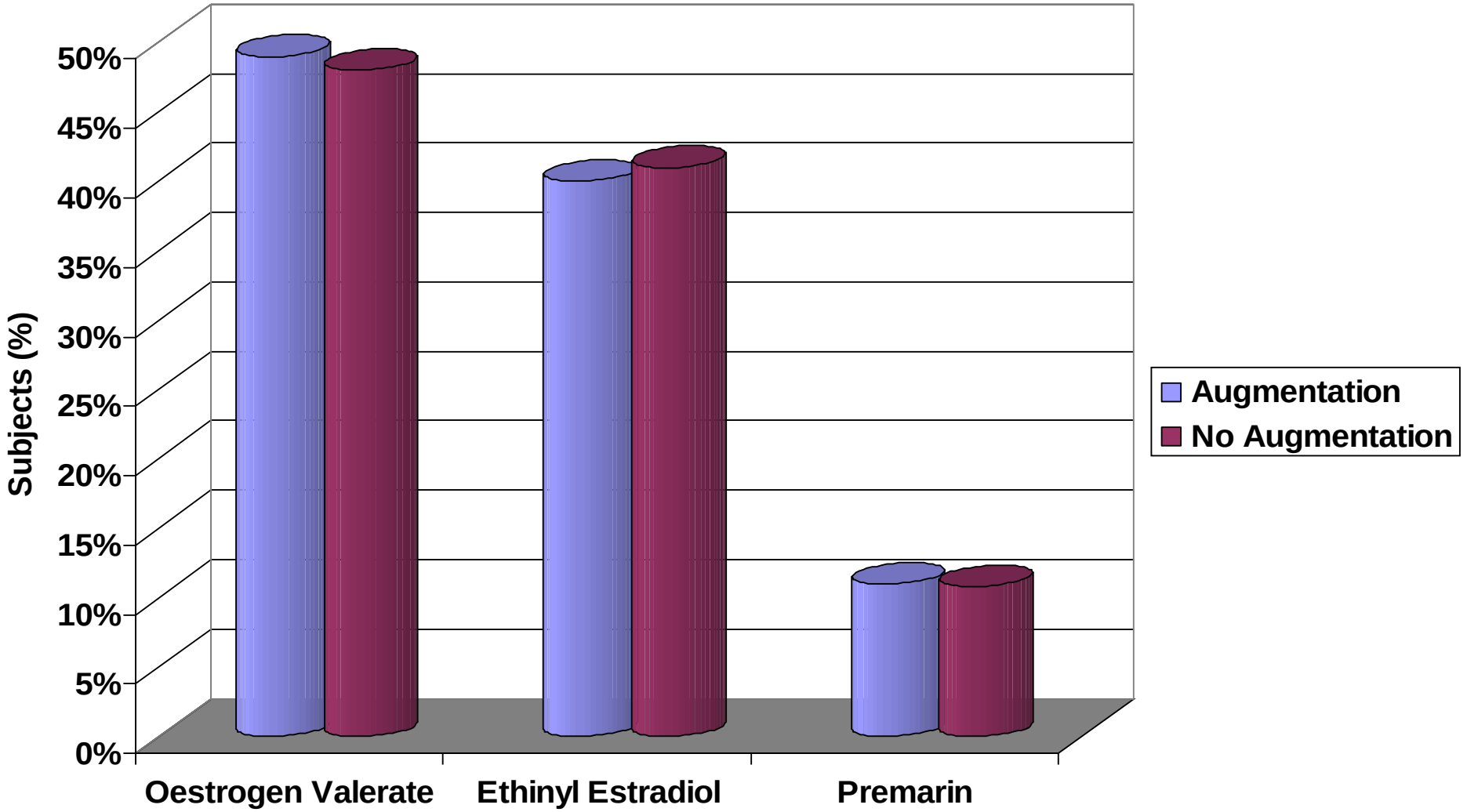
# Need for Augmentation by Oestrogen Type




Seal JECM 2012 *97: 4422-4428*

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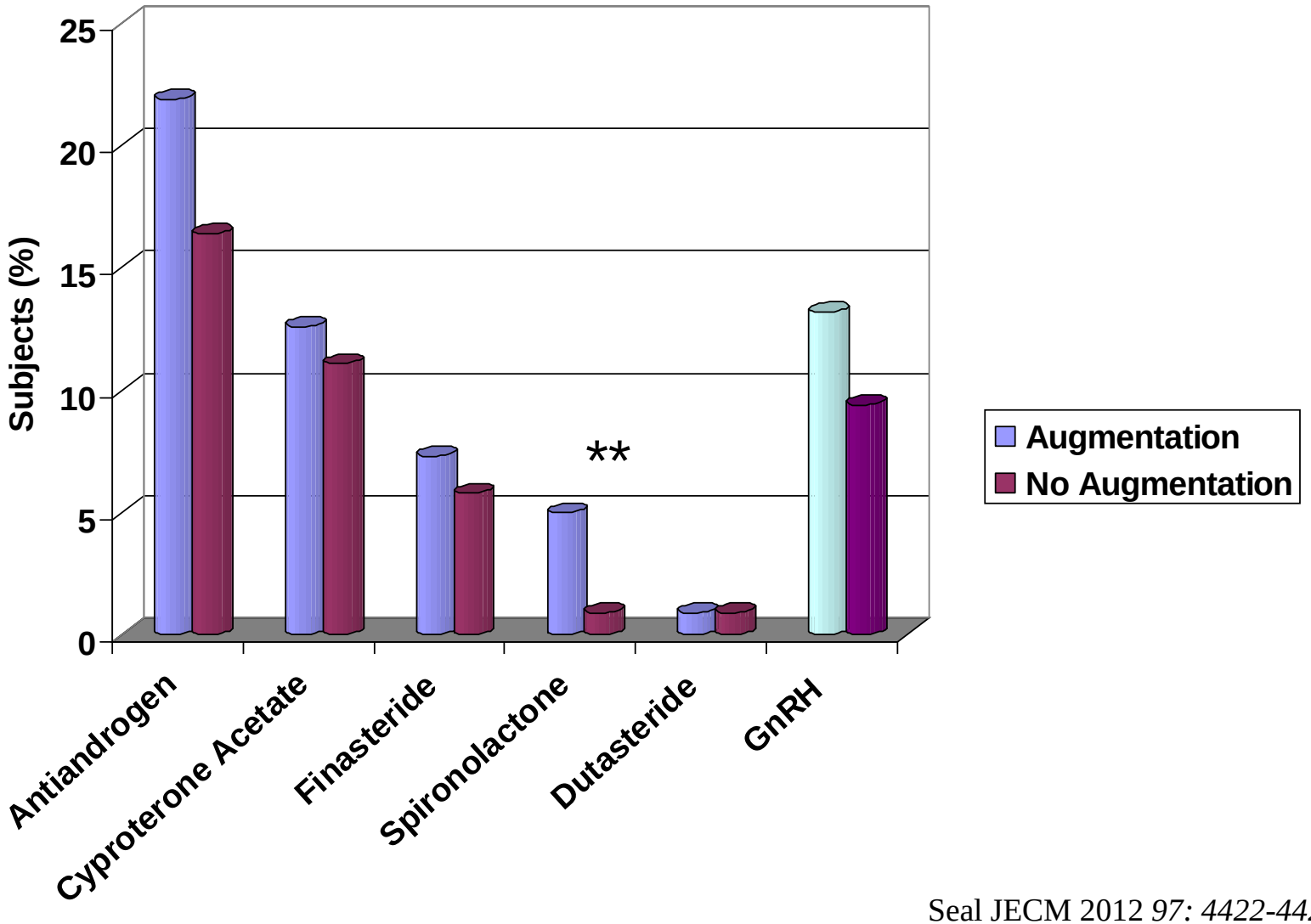
# Need for Augmentation by Testosterone Suppression Type




Seal JECM 2012 *97: 4422-4428*

# Contraindications

- History of Breast Cancer
- Thromboembolism
  - Active
  - Recurrent
- Focal migraine
- Obesity
- Smoking
- Ischaemic heart disease
- Single DVT
- Family history of breast cancer

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# Morbidity in 816 Transwomen

| | No. Observed | SIR (95% CI) |
|---|---|---|
| **Venous thrombosis/PE** | **45** | **19.56 [12.27-26.18]** |
| Postoperative | 5 | |
| After Trauma | 4 | |
| Without Cause | 36 | |
| **Myocardial Infarction (6 fatal)** | **10** | **0.05 [0.24-0.91]** |
| Angina Pectoris | 4 | NA |
| Cerebrovascular Disease | 6 | 1.71 [0.63-3.88] |
| TIA | 5 | |
| Intracranial Haemorrhage | 1 | |
| Occlusion of Leg Artery | 1 | NA |
| Hypertension (>160/95mmHg) | 61 | 0.98 [0.75-1.26] |
| Prostatic Carcinoma | 1 | 0.91 [0.02-5.07] |
| **Elevation of Prolactin (>1000mU//l)** | **115** | **82.14 [67.81-98.95]** |
| Elevation of Liver Enzymes | 88 | |
| Transient (<6 months) | 23 | |
| Persistent (>6 months) | 12 | |
| Hepatitis B | 12 | 44.44 [22.96-77.64] |
| Alcohol related | 16 | |
| Others | 25 | |
| **Cholelithiasis (5 Preexistent)** | **8** | **14.04 [6.22-27.65]** |
| HIV Seroconversion (3 died of AIDS) | 13 | NA |

Van Kesteren Clin Endo 1997 47 337-342

# Morbididty: Male to Female

- Thromboembolism
  - x20 (14%)
  - 60% in first year
  - 0.4% annual incidence
- Hyperprolactinaemia
  - x80
- Gall Stones
  - X5
- MI rate half expected

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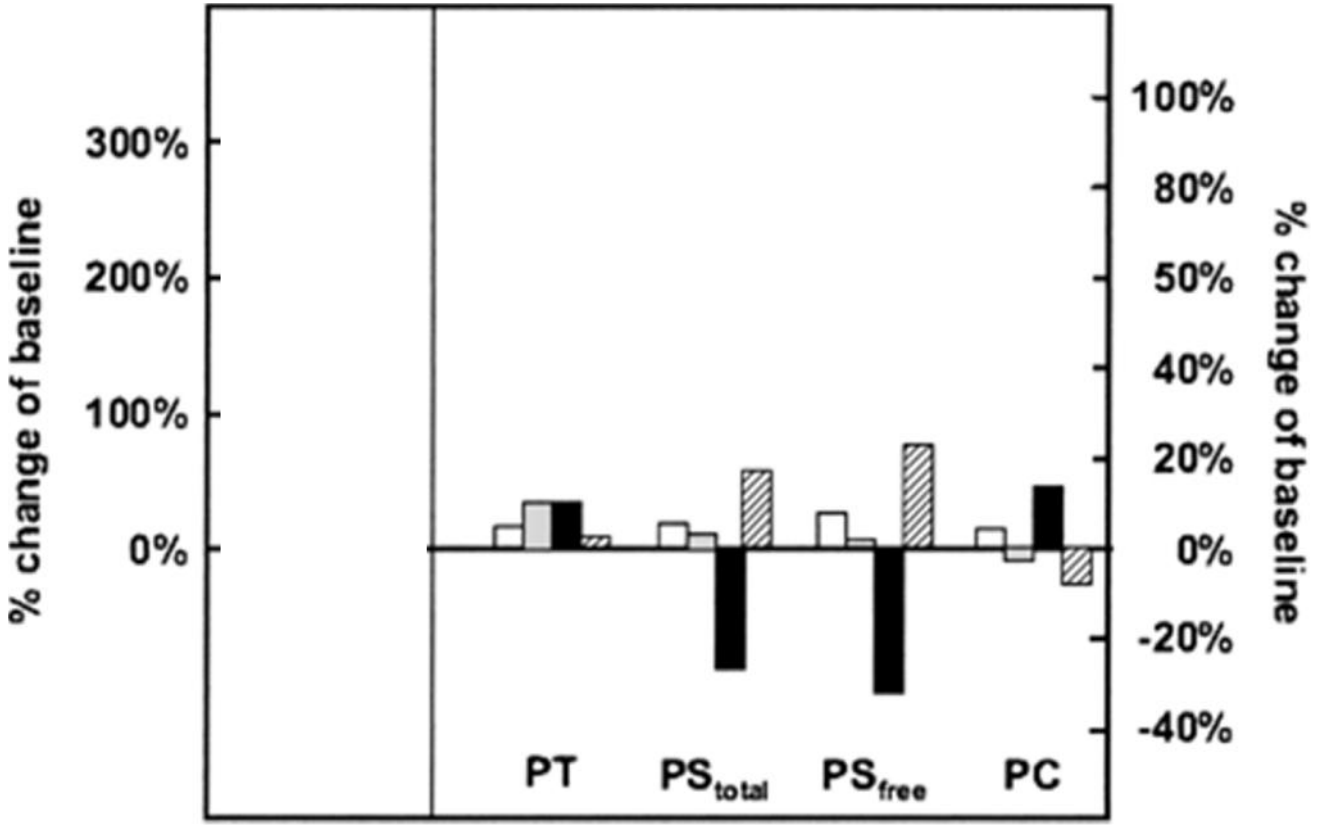
# Effect of Oestrogens on Coagulation factors in Transpeople




**CPA-only (*open bars*), td-E2+CPA (*shaded bars*), and oral-EE+CPA (*solid bars*), F M transsexuals with T esters (*hatched bars*).**

**PT, Prothrombin; PS, protein S; PC, protein C.**

**1 Toorians AW, *J Clin Endocrinol Metab* 2003; 88(12): 5723-9**

# VTE Risk in Women Taking Oral Contraceptive Pill

| Smoking status | OC use | Patients | Control subjects | OR[a] (CI95) |
|---|---|---|---|---|
| Never | no | 105 | 168 | 1 |
| Former | no | 54 | 52 | 1.63 (1.00–2.67) |
| Current | no | 87 | 93 | 2.03 (1.33–3.11) |
| Never | yes | 257 | 189 | 3.90 (2.63–5.79) |
| Former | yes | 82 | 40 | 4.83 (2.89–8.08) |
| Current | yes | 271 | 94 | 8.79 (5.73–13.49) |

Pomp Am J Haematol 2008 83 97-102

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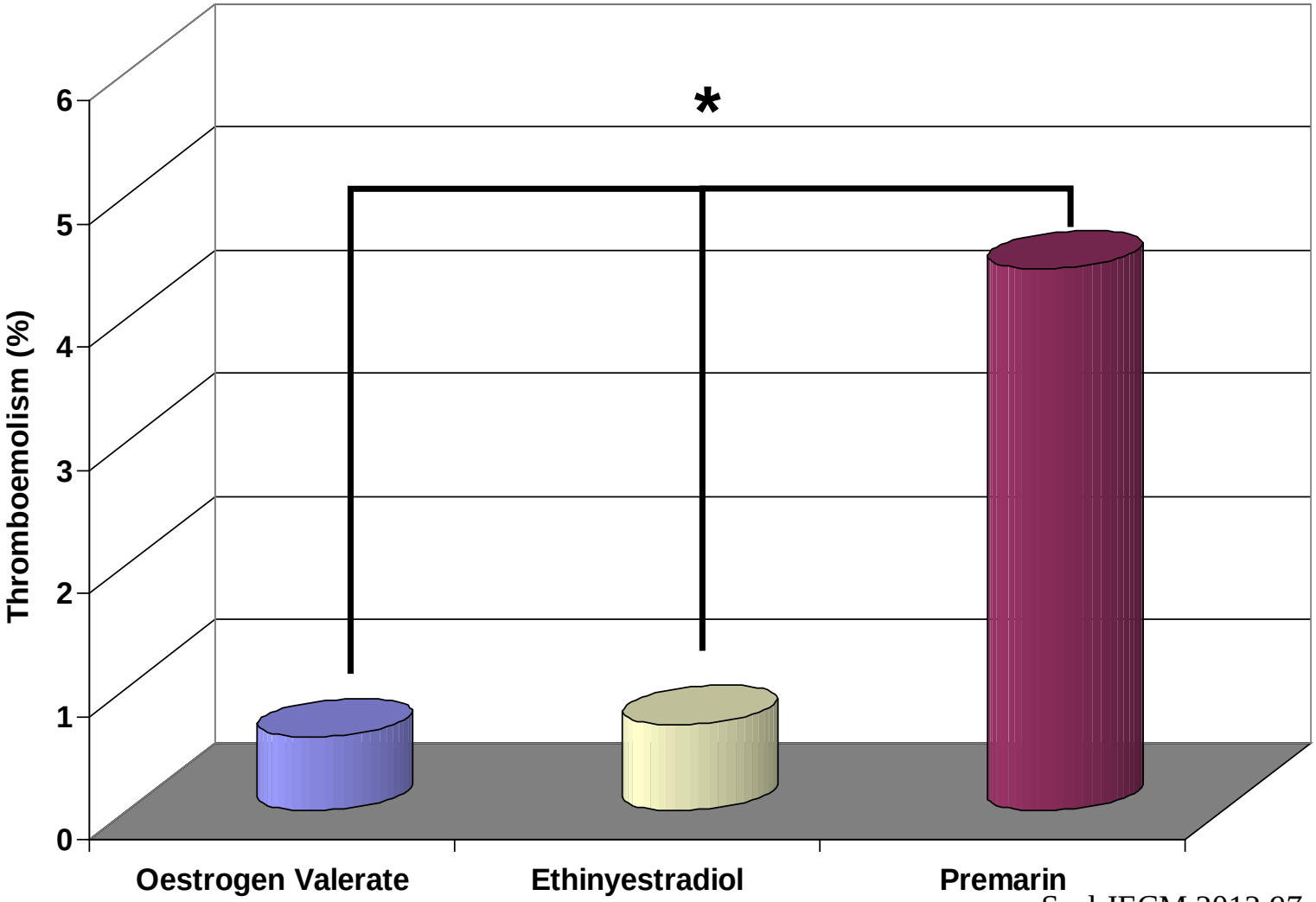
# Thromboembolism Risk By Oestrogen Type




Seal JECM 2012 *97: 4422-4428*

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# Pre Operative

## 3-6 Months

| |
|---|
| Testosterone levels until stable |
| Oestradiol blood level (if on oestrogen valerate) |
| LFT |
| Breast Self examination |
| Blood Pressure |
| Weight |

## 6-12 Months

| |
|---|
| Serum Prolactin |
| ***Over 50*** : |
| PSA |

# Peri- and Post- Operative Management

- Stop oestrogen 6 weeks before surgery
- Continue GnRH
- Doses reduce by half post operatively if on suppressive oestrogen
- Preop Oestrogen dose continued if on GnRH analogues
- Stop GnRH post operatively
- Life long treatment
  - SMR is 1

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# Post Operative

| |
|---|
| Lipids |
| Serum Prolactin |
| LFTs |
| Blood Pressure |
| Weight |
| ***Over 40:*** |
| Consider Transdermal Oestrogen |
| ***Over 50:*** |
| Discuss stopping HRT |
| Mammography every 5 years |
| PSA |
| |
| DEXA scan |

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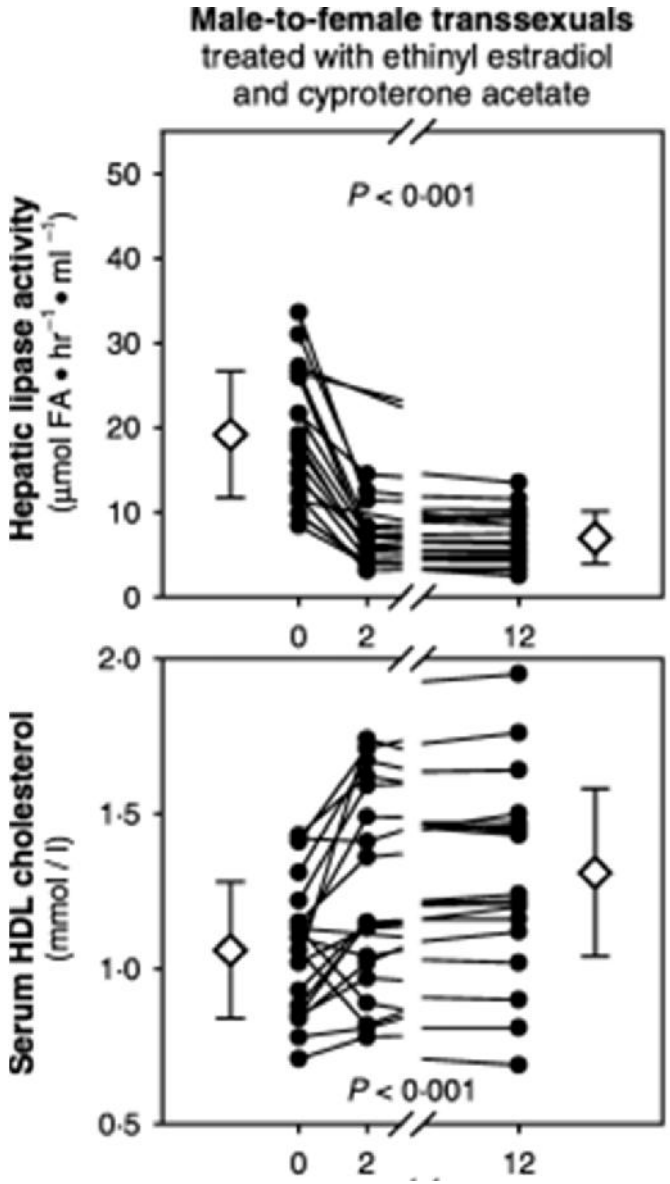
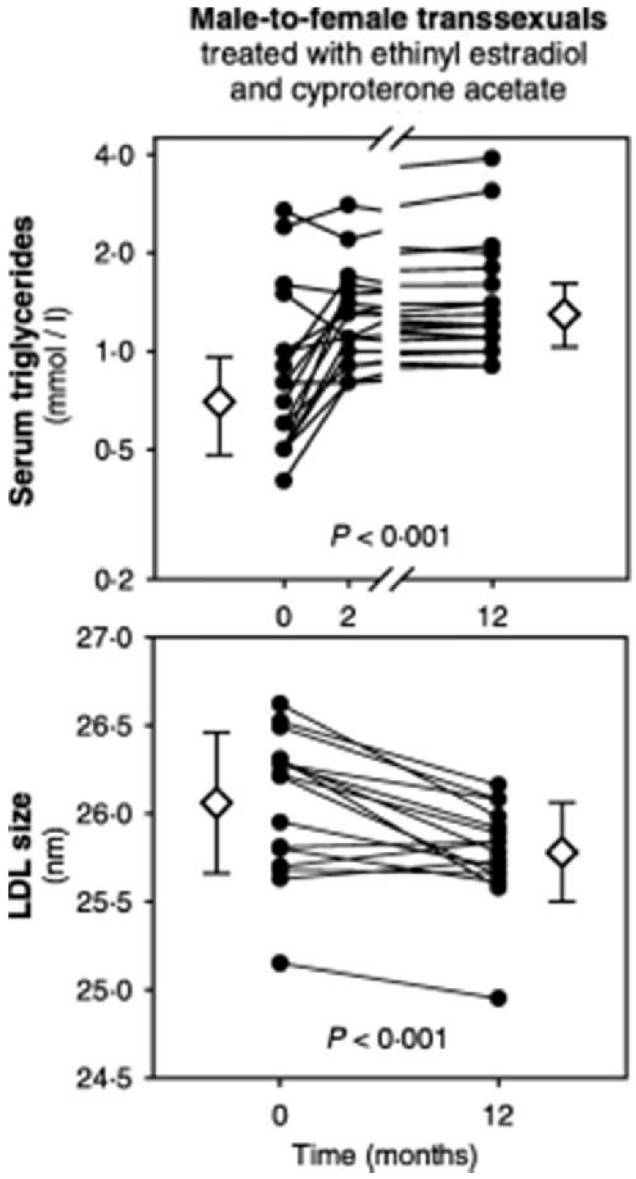
# Side effects of Hormone Treatment in Transwomen

| | Type of oestrogen | | | |
|---|---|---|---|---|
| Adverse event | Oestrogen Valerate N= 163 | Ethinyl Estradiol N= 132 | CEE N= 45 | Total (of population) N=342 |
| Depression | 28.8 | 24.6 | 24.4 | 26.6 |
| Thromboembolism | 0.6 | 0.7 | 4.4* | 1.2 |
| Flushing | 4.3 | 3.0 | 3.5 | 3.5 |
| Hair Loss | 2.5* | 0.0 | 0.0 | 1.2 |
| Hyperprolactinaemia | 1.8 | 3.0 | 2.2 | 2.3 |
| Hypertension | 3.7 | 1.5 | 2.2 | 2.6 |
| Diabetes | 0.3 | 0.0 | 0.0 | 0.3 |
| Abnormal Liver Function | 1.2 | 0.9 | 0.0 | 2.0 |

Seal JECM 2012 *97: 4422-4428*




Elbers Clin Endo 2003 58 562-71




Elbers Clin Endo 2003 58 562-71

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# Other Therapies

| | |
|---|---|
| ■ Anti androgens<br>– Cyproterone acetate<br>– Finasteride | ■ Abnormal LFT<br>■ Liver Tumours<br>■ Depression |
| ■ Oestrogen receptor agonists<br>– Spironolactone | ■ Abnormal U +E<br>■ Abnormal LFT<br>■ Hyperkallaemia |
| ■ GnRH analogues | ■ Menopausal symptoms |

# Progesterone

- Plays no role in puberty
  - Ovulation generally starts 18months after menarche when breast development is complete
- Lowers Mood
- Inhibits oestrogen induced proliferation
- Combined Estrogen, Progestin HRT
  - Increases risk of Breast cancer
  - Increase Risk of Stroke
  - Increases rick of MI

| | Women aged ~50–59 years | Women aged ~60–69 years |
|---|---|---|
| **Excess incidence per 1000 HRT users, over 5-year period, for:** | | |
| Breast cancer | 3·2 | 4·0 |
| Stroke | 1·2 | 4·0 |
| Pulmonary embolism | 1·6 | 4·0 |
| *Total excess** | *~6 per 1000, ~1 in 170 users* | *~12 per 1000, ~1 in 80 users* |
| **Reduction in incidence per 1000 HRT users, over 5-year period, for:** | | |
| Colorectal cancer | 1·2 | 3·0 |
| Fracture of neck of femur | 0·5 | 2·5 |
| *Total deficit** | *~1·7 per 1000, ~1 in 600 users* | *~5·5 per 1000, ~1 in 180 users* |
| **Overall balance*** | **Net excess:** *~4·3 per 1000, ~1 in 230 users* | **Net excess:** *~6·5 per 1000, ~1 in 150 users* |

*Giving equal weight to each type of event.

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# Transmen

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# Testosterone Effects in Transmen

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

Hembree JCEM 2009, 94(9):3132–3154

# Route of Administration

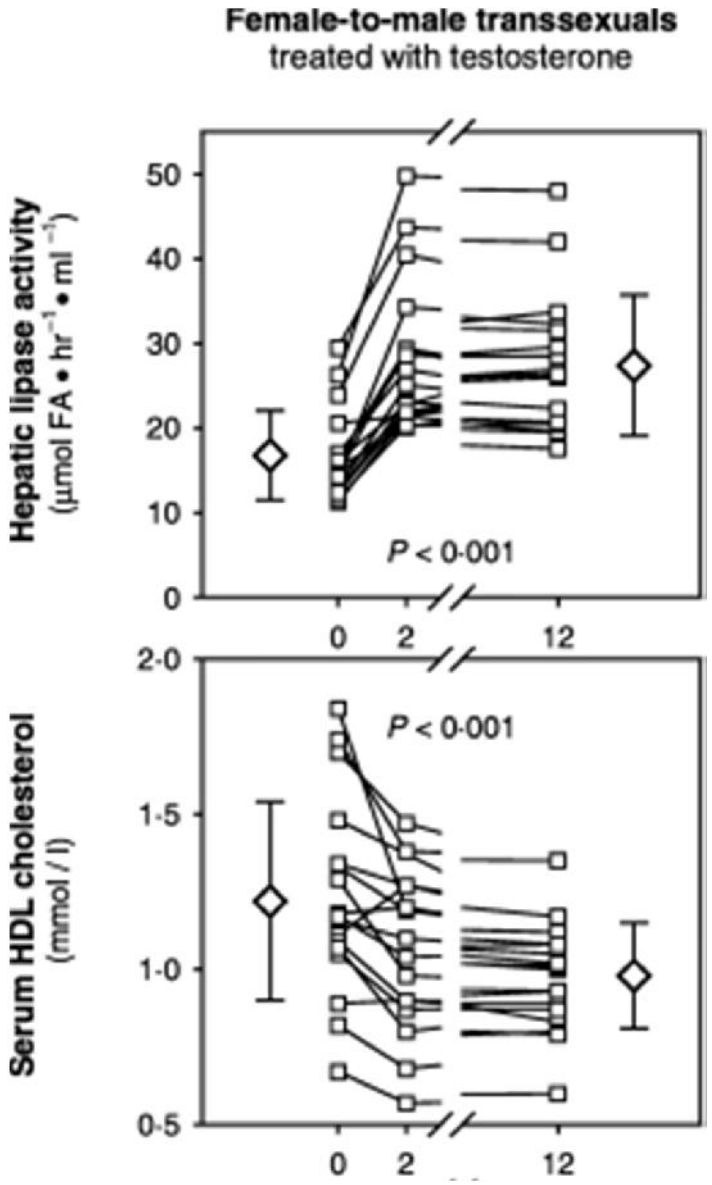
- ORAL
  - Testosterone undecanoate (120-240mg/day)
- INTRAMUSCULAR
  - Sustenon (250mg im 2-4 weekly) Licensed
  - Primoteston (100mg 1-2 weekly)
  - Nebido (1000mg 12 weekly)
- TRANSDERMAL
  - Patch (5mg to 7.5mg)
  - Gel (50mg)
- SUBCUTANEOUS IMPLANTS
  - 600-1200mg

# Charing Cross Regimen

- INTRAMUSCULAR
  - Sustenon (250mg im 2-4 weekly)
    **Licensed**
  - Nebido (1000mg 12 weekly)
- TRANSDERMAL
  - Gel (50-100mg)
- SUBCUTANEOUS IMPLANTS
  - 600-1200mg

# Haematological Effects of Androgen Therapy

- Testosterone increases erythropoietin
- Hematocrit increases with androgen therapy
  - 12 -25%.
- 3-5% require phlebotomy or stop therapy
- Immune function not effected

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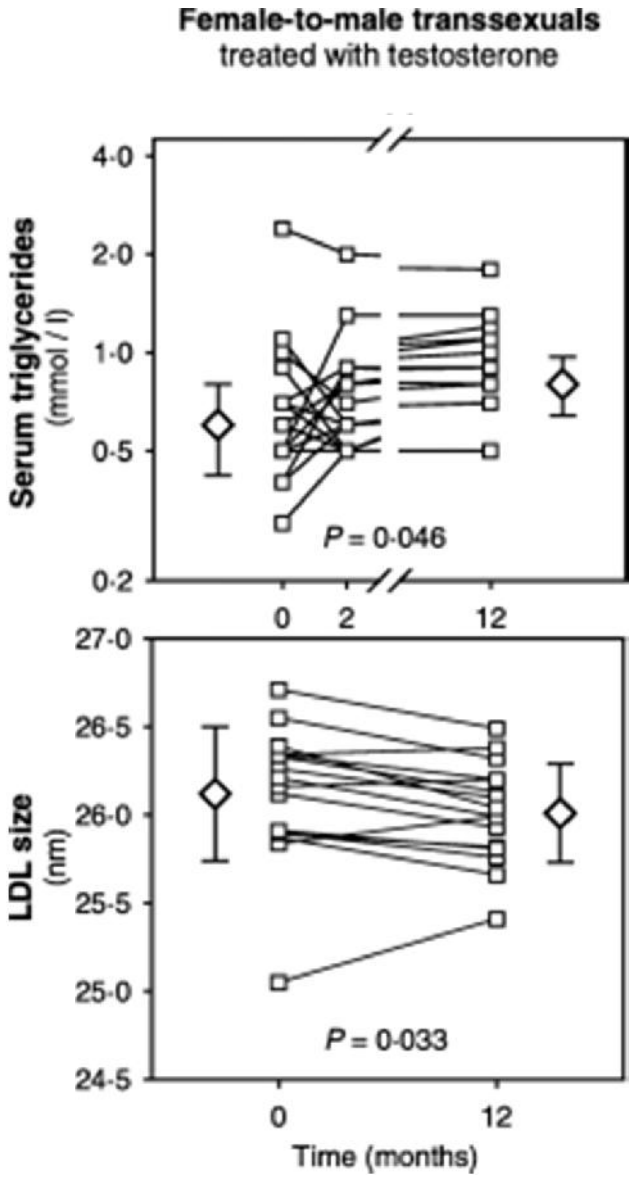


Elbers Clin Endo 2003 58 562-71

# Testosterone and Endometrial Hyperplasia

- Endometrial hyperplasia occurs in 15%
- Recommend hysterectomy and salpingoopherectomy after 2 years of treatment

Futterweit 1998 Arch Sex Behav27 209-226

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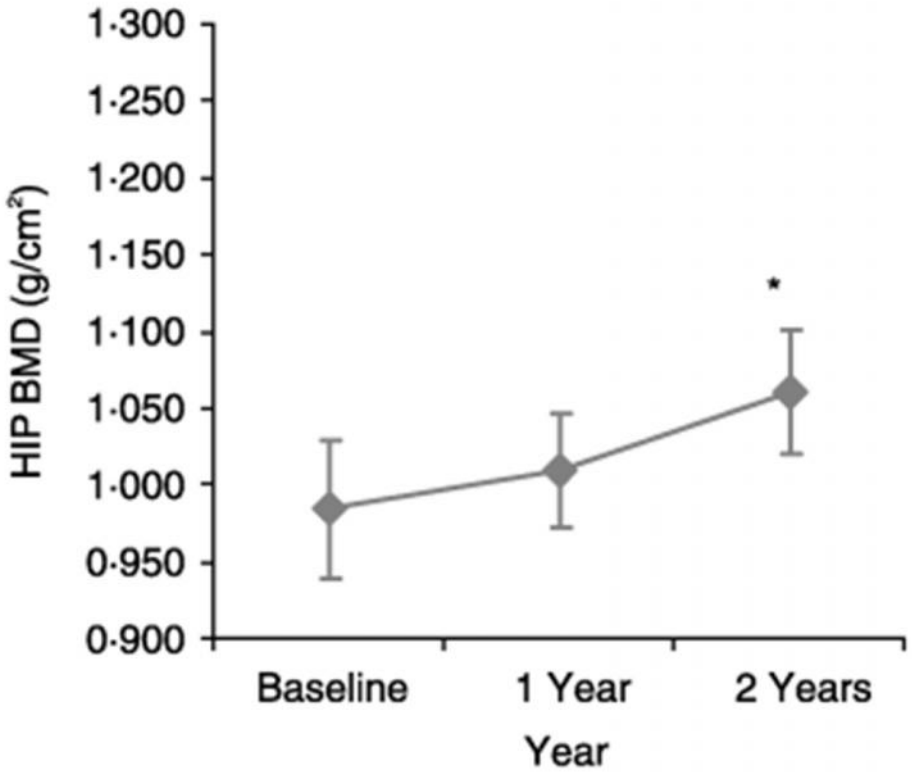
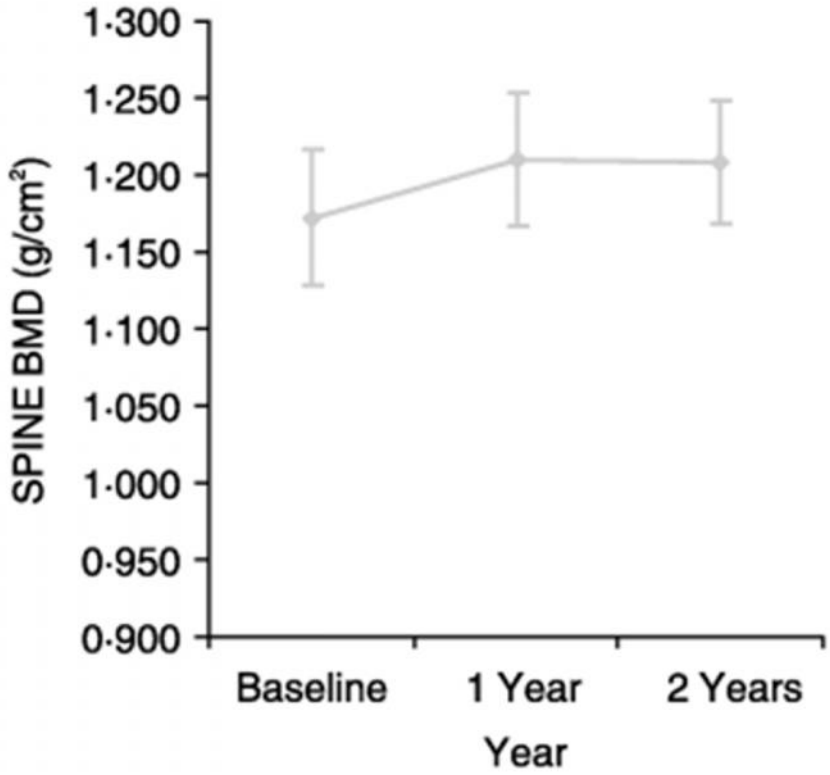
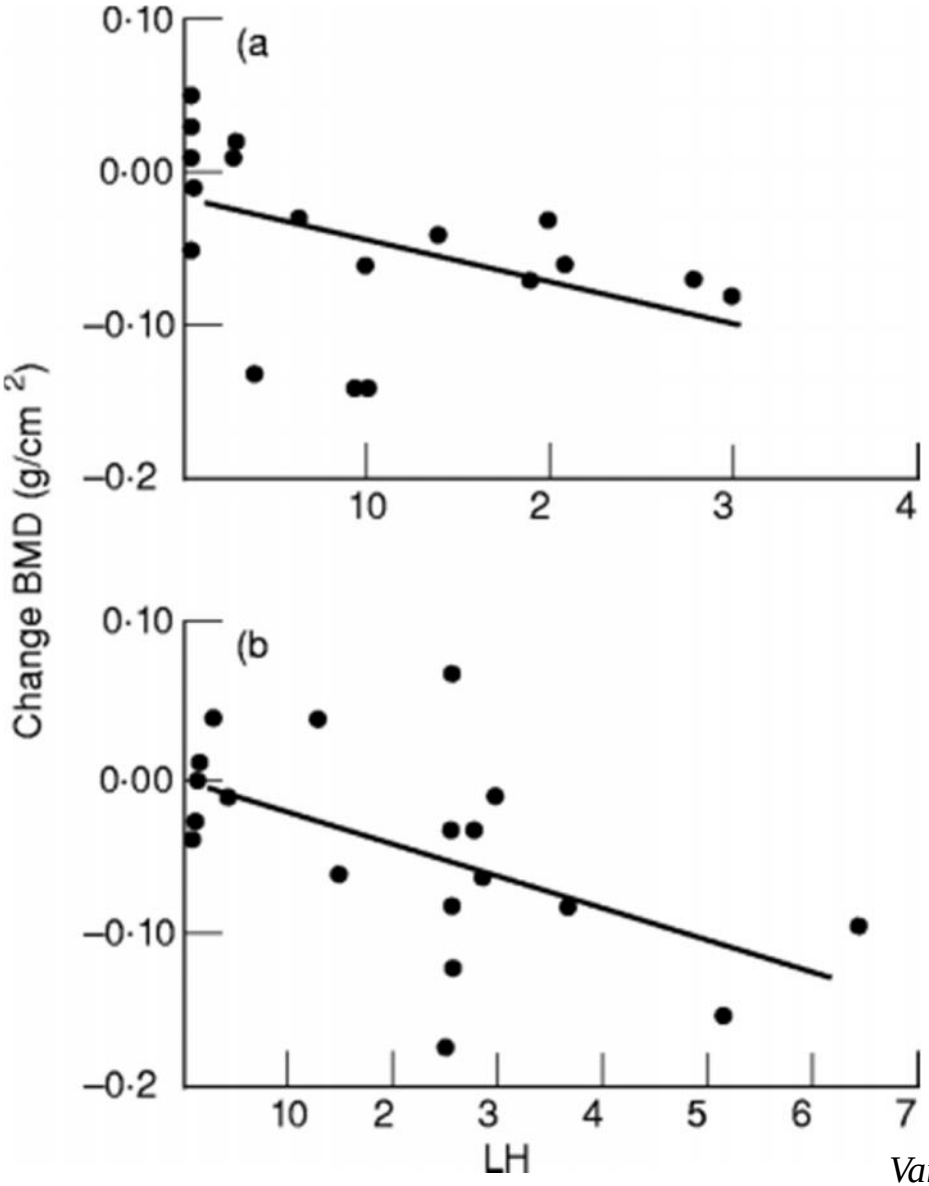
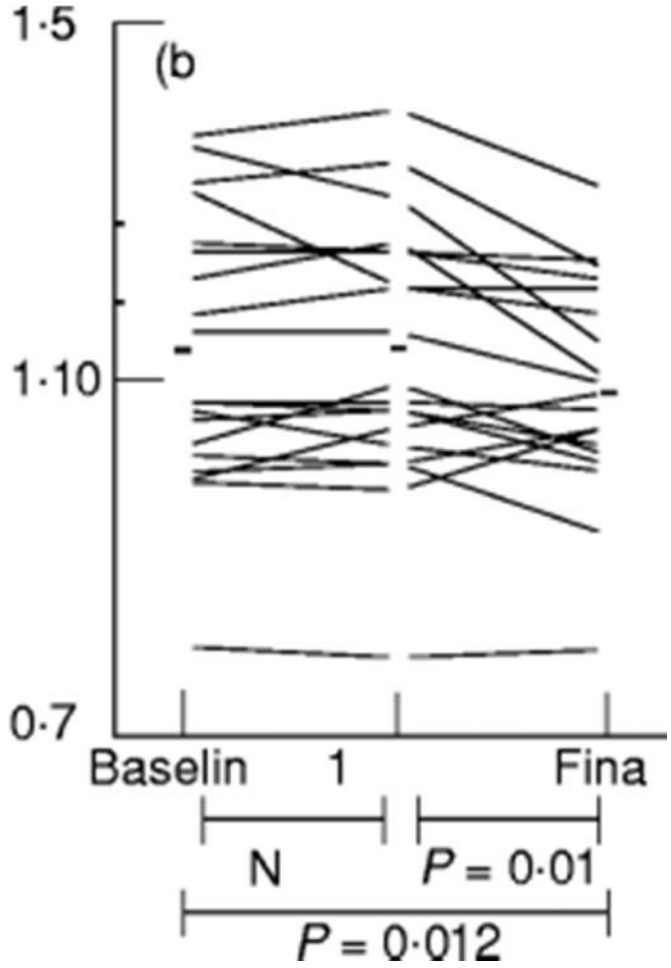
# BMD in Transmen




*Turner 2004 Clin Endocrinol* **61** (5), 560-566




FtM

*Van Kesteren 1998 Clinical Endocrinology* **48** (3), 347-354

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# Monitoring of Testosterone Replacement Therapy 1

- i. m .
  - Pre injection and 1 week post injection
  - Or testosterone week 10, 11, 12
- Transdermal Patch
  - 8 hours post application
- Gel
  - plasma testosterone 4 hours after application
- Oral
  - Dihydrotestosterone levels
- Buccal
  - Testostereone 4 hours after application

# Monitoring of Testosterone Replacement Therapy 1

- Testosterone aim for mid normal range
- IN ALL annual
  - FBC
  - Profile
  - Lipids
  - glucose
  - ?? DEXA

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# Pre Operative

## 3-6 Months

| |
|---|
| Lipid Profile |
| FBC (polycythaemia) |
| Testosterone levels |
| LFTs |
| Blood Pressure |
| Weight |

| |
|---|
| Cervical smear (3 years) |
| Endometrial US (every 2y) |

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# Post Operative

| |
|---|
| Decrease testosterone to standard HRT dose |
| Lipid Profile |
| FBC (polycythaemia) |
| Testosterone levels |
| LFTs |
| Blood Pressure |
| Weight |
| (DEXA scan) |

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# Morbidity in 293 Transmen

| | No. Observed | SIR (95% CI) |
|---|---|---|
| Myocardial Infarction (6 fatal) | 1 | 0.34 [0.01-1.92] |
| Angina Pectoris | 1 | NA |
| Hypertension (>160/95mmHg) | 12 | 1. 2[0.43-1.47] |
| Elevation of Liver Enzymes | 45 | |
| Transient (<6 months) | 13 | |
| Persistent (>6 months) | 20 | |
| Alcohol related | 3 | |
| Others | 9 | |
| Acne | 80 | NA |
| Venous thrombosis | 1 | 9.09 [0.23-50.65] |
| Postoperative | | |
| Oedema | 5 | NA |

Van Kesteren Clin Endo 1997 47 337-342

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## Table 1. Baseline characteristics among sex-reassigned subjects in Sweden (N=324) and population controls matched for birth year and sex.

| Characteristic at baseline | Sex-reassigned subjects (N = 324) | Birth-sex matched controls (N = 3,240) | Final-sex matched controls (N = 3,240) |
|---|---|---|---|
| Gender | | | |
| Female at birth, male after sex change | 133 (41%) | 1,330 (41%) | 1,330 (41%) |
| Male at birth, female after sex change | 191 (59%) | 1,910 (59%) | 1,910 (59%) |
| Average age at study entry [years] (SD, min-max) | | | |
| Female at birth, male after sex change | 33.3 (8.7, 20–62) | 33.3 (8.7, 20–62) | 33.3 (8.7, 20–62) |
| Male at birth, female after sex change | 36.3 (10.1, 21–69) | 36.3 (10.1, 21–69) | 36.3 (10.1, 21–69) |
| Both genders | 35.1 (9.7, 20–69) | 35.1 (9.7, 20–69) | 35.1 (9.7, 20–69) |
| Immigrant status | | | |
| Female at birth, male after sex change | 28 (21%) | 118 (9%) | 100 (8%) |
| Male at birth, female after sex change | 42 (22%) | 176 (9%) | 164 (9%) |
| Both genders | 70 (22%) | 294 (9%) | 264 (8%) |
| Less than 10 years of schooling prior to entry vs. 10 years or more | | | |
| Females at birth, males after sex change | 49 (44%); 62 (56%) | 414 (37%); 714 (63%) | 407 (36%); 713 (64%) |
| Males at birth, females after sex change | 61 (41%); 89 (59%) | 665 (40%); 1,011 (60%) | 595 (35%); 1,091 (65%) |
| All individuals with data | 110 (42%); 151 (58%) | 1,079 (38%); 1,725 (62%) | 1,002 (36%); 1,804 (64%) |
| Psychiatric morbidity* prior to study entry | | | |
| Female at birth, male after sex change | 22 (17%) | 47 (4%) | 42 (3%) |
| Male at birth, female after sex change | 36 (19%) | 76 (4%) | 72 (4%) |
| Both genders | 58 (18%) | 123 (4%) | 114 (4%) |
| Rural [vs. urban] living area prior to entry | | | |
| Female at birth, male after sex change | 13 (10%) | 180 (14%) | 195 (15%) |
| Male at birth, female after sex change | 20 (10%) | 319 (17%) | 272 (14%) |
| Both genders | 33 (10%) | 499 (15%) | 467 (14%) |

**Note:**
*Hospitalizations for gender identity disorder were not included.
doi:10.1371/journal.pone.0016885.t001

Dhejne C, Lichtenstein P, Boman M, Johansson ALV, et al. (2011) Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden. PLoS ONE 6(2): e16885. doi:10.1371/journal.pone.0016885
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0016885

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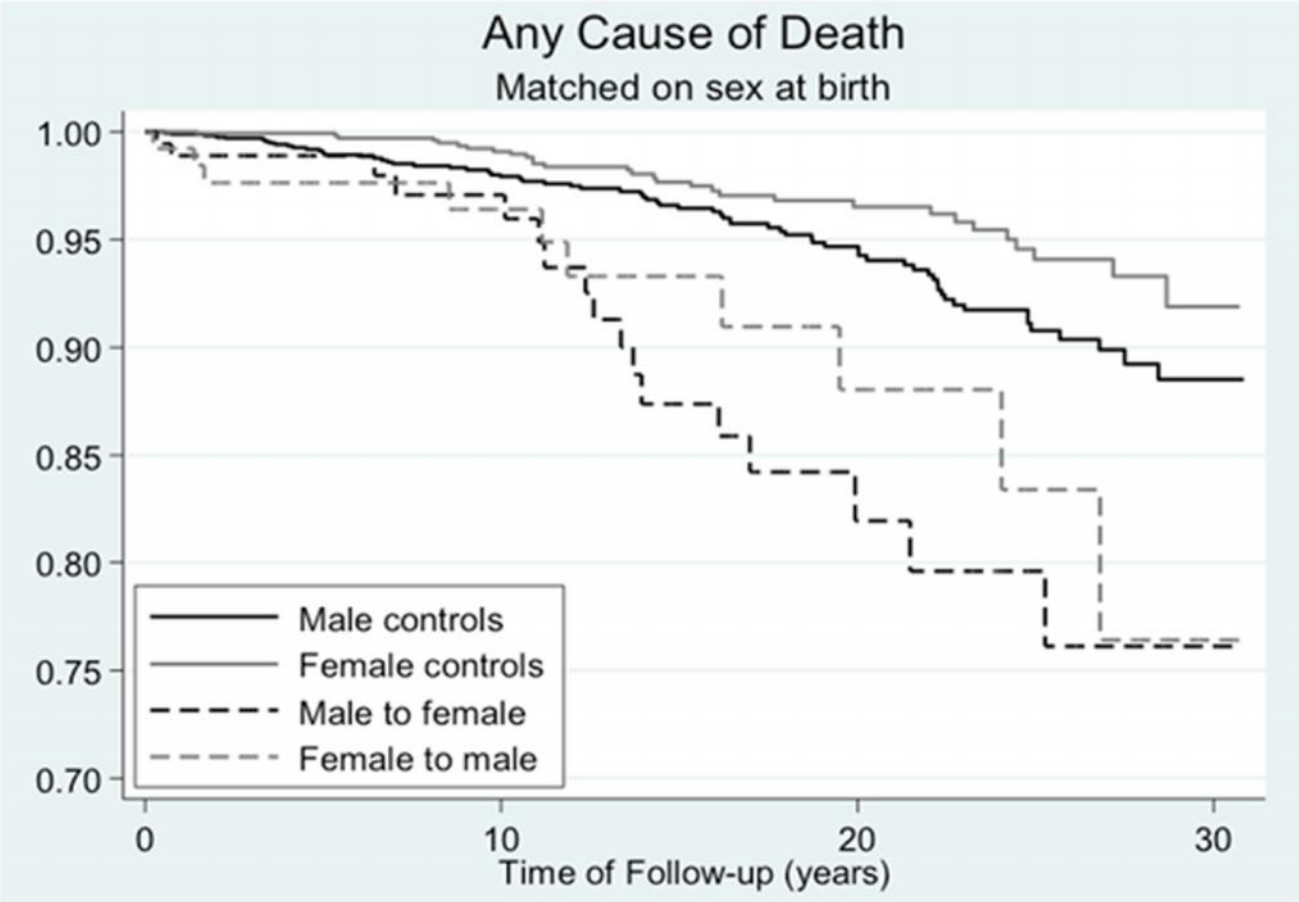
**Death from any cause as a function of time after sex reassignment among 324 transsexual persons in Sweden (male-to-female: N=191, female-to-male: N=133), and population controls matched on birth year.**




Dhejne C, Lichtenstein P, Boman M, Johansson ALV, et al. (2011) Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden. PLoS ONE 6(2): e16885. doi:10.1371/journal.pone.0016885
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## Risk of various outcomes among sex-reassigned subjects in Sweden (N=324) compared to population controls matched for birth year and birth sex.

| | Number of events cases/ controls 1973–2003 | Outcome incidence rate per 1000 person-years 1973–2003 (95% CI) | | Crude hazard ratio (95% CI) 1973–2003 | Adjusted* hazard ratio (95% CI) 1973–2003 | Adjusted* hazard ratio (95% CI) 1973–1988 | Adjusted* hazard ratio (95% CI) 1989–2003 |
|---|---|---|---|---|---|---|---|
| | | Cases | Controls | | | | |
| Any death | 27/99 | 7.3 (5.0–10.6) | 2.5 (2.0–3.0) | 2.9 (1.9–4.5) | 2.8 (1.8–4.3) | 3.1 (1.9–5.0) | 1.9 (0.7–5.0) |
| Death by suicide | 10/5 | 2.7 (1.5–5.0) | 0.1 (0.1–0.3) | 19.1 (6.5–55.9) | 19.1 (5.8–62.9) | N/A | N/A |
| Death by cardiovascular disease | 9/42 | 2.4 (1.3–4.7) | 1.1 (0.8–1.4) | 2.6 (1.2–5.4) | 2.5 (1.2–5.3) | N/A | N/A |
| Death by neoplasm | 8/38 | 2.2 (1.1–4.3) | 1.0 (0.7–1.3) | 2.1 (1.0–4.6) | 2.1 (1.0–4.6) | N/A | N/A |
| Any psychiatric hospitalisation‡ | 64/173 | 19.0 (14.8–24.2) | 4.2 (3.6–4.9) | 4.2 (3.1–5.6) | 2.8 (2.0–3.9) | 3.0 (1.9–4.6) | 2.5 (1.4–4.2) |
| Substance misuse | 22/78 | 5.9 (3.9–8.9) | 1.8 (1.5–2.3) | 3.0 (1.9–4.9) | 1.7 (1.0–3.1) | N/A | N/A |
| Suicide attempt | 29/44 | 7.9 (5.5–11.4) | 1.0 (0.8–1.4) | 7.6 (4.7–12.4) | 4.9 (2.9–8.5) | 7.9 (4.1–15.3) | 2.0 (0.7–5.3) |
| Any accident | 32/233 | 9.0 (6.3–12.7) | 5.7 (5.0–6.5) | 1.6 (1.1–2.3) | 1.4 (1.0–2.1) | 1.6 (1.0–2.5) | 1.1 (0.5–2.2) |
| Any crime | 60/350 | 18.5 (14.3–23.8) | 9.0 (8.1–10.0) | 1.9 (1.4–2.5) | 1.3 (1.0–1.8) | 1.6 (1.1–2.4) | 0.9 (0.6–1.5) |
| Violent crime | 14/61 | 3.6 (2.1–6.1) | 1.4 (1.1–1.8) | 2.7 (1.5–4.9) | 1.5 (0.8–3.0) | N/A | N/A |

**Notes:**
*Adjusted for psychiatric morbidity prior to baseline and immigrant status.
‡Hospitalisations for gender identity disorder were excluded.
N/A Not applicable due to sparse data.
doi:10.1371/journal.pone.0016885.t002

Dhejne C, Lichtenstein P, Boman M, Johansson ALV, et al. (2011) Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden. PLoS ONE 6(2): e16885. doi:10.1371/journal.pone.0016885
http://www.plosone.org/article/info:doi/10.1371/journal.pone.0016885

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# SMR adjusted for age and period of follow-up on hormone treatment by biological sex in 1331 transsexual subjects

| | Male-to-female transsexuals | | Female-to-male transsexuals | |
|---|---|---|---|---|
| Cause of death | Observed cases | SMR (95% CI) | Observed cases | SMR (95% CI) |
| Malignant neoplasm | 28 | 0.98 (0.88–1.08) | 5 | 0.99 (0.65–1.44) |
| Lung | 13 | 1.35 (1.14–1.58) | 1 | 1.06 (0.26–3.19) |
| Digestive tract | 3 | 0.42 (0.28–0.60) | 2 | 2.41 (0.90–5.18) |
| Hematological | 6 | 2.58 (1.97–3.30) | 1 | 2.86 (0.69–8.57) |
| Brain | 2 | 1.59 (0.95–2.46) | 0 | – |
| Other: kidney, melanoma, bone, and prostate in MtF. In FtM: leiomyosarcoma | 4 | 0.79 (0.57–1.07) | 1 | 0.77 (0.25–1.77) |
| Ischemic heart disease | 18 | 1.64 (1.43–1.87) | 1 | 1.19 (0.39–2.74) |
| Cerebrovascular accidents | 5 | 1.26 (0.93–1.64) | 0 | – |
| AIDS | 16 | 30.20 (26.0–34.7) | 0 | – |
| Endocrine/diabetes | 2 | 0.85 (0.41–1.32) | 0 | – |
| Respiratory system diseases | 4 | 0.85 (0.61–1.14) | 0 | – |
| Digestive system diseases | 3 | 1.01 (0.68–1.45) | 1 | 2.56 (0.62–7.69) |
| Genitourinary system disease (ESRD) | 1 | 1.21 (0.58–2.17) | 0 | – |
| Nervous system disease (MS) | 0 | | 1 | 3.57 (0.86–10.7) |
| External causes | 24 | 7.67 (6.84–8.56) | 2 | 2.22 (1.07–5.44) |
| Illicit drugs use | 5 | 13.20 (9.70–17.6) | 1 | 25.00 (6.00–32.5) |
| Suicide | 17 | 5.70 (4.93–6.54) | 1 | 2.22 (0.53–6.18) |
| Unknown/ill-defined symptoms | 21 | 4.00 (3.52–4.51) | 2 | 2.08 (0.69–4.79) |
| Total | 122 | 1.51 (1.47–1.55) | 12 | 1.12 (0.89–1.59) |

ESRD, end-stage renal disease; MS, multiple sclerosis.

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# Hazard ratios (95% CIs) of mortality according to the use of ethinyl estradiol in 964 Transwomen (median follow up of 18.6 years)

| | Use of ethinyl estradiol | | |
|---|---|---|---|
| | Never or former use | Continuous use | *P* value |
| No. of male-to-female transsexuals | 596 | 368 | |
| All-cause mortality | 69 (11.6%) | 51 (13.9%) | |
| Crude | 1.00 | 1.13 (0.78–1.62) | 0.53 |
| Adjusted for age and smoking | 1.00 | 1.33 (0.92–1.92) | 0.13 |
| Fully adjusted[a] | 1.00 | 1.28 (0.88–1.86) | 0.20 |
| Cardiovascular mortality | 8 (1.3%) | 15 (4.1%) | |
| Crude | 1.00 | 2.82 (1.19–6.65) | 0.02 |
| Adjusted for age and smoking | 1.00 | 3.64 (1.52–8.73) | 0.004 |
| Fully adjusted[a] | 1.00 | 3.12 (1.28–7.63) | 0.01 |
| Mortality due to external causes[b] | 12 (2.0%) | 11 (3.0%) | |
| Crude | 1.00 | 1.40 (0.62–3.17) | 0.43 |
| Adjusted for age and smoking | 1.00 | 1.44 (0.63–3.30) | 0.38 |
| Fully adjusted[a] | 1.00 | 1.36 (0.60–3.10) | 0.46 |
| Cancer mortality | 17 (2.9%) | 11 (3.0%) | |
| Crude | 1.00 | 0.99 (0.46–2.12) | 0.98 |
| Adjusted for age and smoking | 1.00 | 1.24 (0.57–2.67) | 0.59 |
| Fully adjusted[a] | 1.00 | 1.35 (0.61–3.00) | 0.46 |
| Non-cardiovascular mortality | 46 (7.7%) | 30 (8.2%) | |
| Crude | 1.00 | 1.00 (0.63–1.59) | 0.99 |
| Adjusted for age and smoking | 1.00 | 1.16 (0.73–1.84) | 0.54 |
| Fully adjusted[a] | 1.00 | 1.15 (0.71–1.83) | 0.58 |

*P* values using Cox proportional hazards models.
[a]Adjusted for age, smoking status, and a starting date before 1990 (because before 1990, ethinyl estradiol was the standard estrogen prescribed).
[b]Deaths due to accidents, intentional self-harm and suicide, assault, drugs, and adverse effects.

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# Long Term Outcome in Gender Dysphoria

- There is no difference in SMR for transmen
- There may be an increase in SMR for transwomen
  - Suicide
  - HIV
  - Cardiovascular disease
    - Ethinylestradiol users
- However Studies are confounded by changes in therapy over the last 10 years

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# Long Term Monitoring in Transwomen

- Routine cancer screening recommended as for non-transsexual individuals (breasts, colon, prostate).
- Consider BMD testing at baseline if risk factors for osteoporotic fracture are present
- In individuals at low risk, screening for osteoporosis should be conducted at age 60 or in those who are not compliant with hormone therapy

Hembree JCEM 2009, 94(9):3132–3154

- Cardiovascular Risk Intervention is important
- Psychological support should be offered when needed

# Long Term Monitoring of Transmen

- Consider BMD testing at baseline if risk factors for osteoporotic fracture are present
- In individuals at low risk, screening for osteoporosis should be conducted at age 60 or in those who are not compliant with hormone therapy.
- If cervical tissue is present, cervical sceening according to local recommendations.
- If mastectomy is not performed, then consider mammograms as local organisations

Hembree JCEM 2009, 94(9):3132–3154

# In Summary

- Gender dysphoria requires hormonal therapy to achieve the secondary sexual characteristics of the desired gender
- Hormonal therapy
  - carries physical risks
  - provides psychological benefit
- Careful monitoring is required to prevent complications occurring
- Hormonal therapy in gender dysphoria is
  - Effective
  - Safe

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# Morbididty: Female to male

- No excess mortality
- No excess morbidity

- ACNE

- MI rate one third expected

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## Baseline and treatment-related characteristics of 1331 transpeople who underwent cross-sex hormone treatment.

| | Male-to-female transsexuals | Female-to-male transsexuals |
|---|---|---|
| *n* | 966 | 365 |
| Age at start (mean ± S.D.) | 31.4 ± 11.4 | 26.1 ± 7.6 |
| Range (years of age) | 16–76 | 16–56 |
| Age groups (*n* (%)) | | |
| 15–24 | 329 (34.1) | 204 (55.9) |
| 25–39 | 429 (44.4) | 145 (39.7) |
| 40–64 | 199 (20.6) | 16 (4.4) |
| 65–80 | 9 (0.9) | 0 |
| Smoking status (*n* (%)) | | |
| Never | 254 (26.3) | 94 (25.8) |
| Current | 373 (38.6) | 131 (35.9) |
| Former or unknown | 339 (35.1) | 140 (38.3) |
| Starting date before 1990 (*n* (%)) | 619 (64.2) | 197 (54.0) |
| Sex reassignment surgery (*n* (%)) | 834 (86.7) | 343 (94.0) |
| Follow-up on hormone treatment (years ± S.D.) | 19.4 ± 7.7 | 18.8 ± 6.3 |
| <5 years (*n* (%)) | 22 (2.2) | 1 (0.3) |
| 5–10 years (*n* (%)) | 50 (5.2) | 6 (1.6) |
| 10–15 years (*n* (%)) | 229 (23.7) | 111 (30.4) |
| 15–20 years (*n* (%)) | 252 (26.1) | 99 (27.2) |
| 20–25 years (*n* (%)) | 190 (19.7) | 86 (23.5) |
| 25–30 years (*n* (%)) | 131 (13.6) | 43 (11.8) |
| >30 years (*n* (%)) | 92 (9.5) | 19 (5.2) |

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| | Male-to-female transsexual people | | | Female-to-male transsexual people | | |
|---|---|---|---|---|---|---|
| | Effect | Evidence | N | Effect | Evidence | N |
| Positive effects | Gynecomastia | Observational (27) | 28 | Deepened voice | Observational (12) | 122 |
| | Enlarged areolae and nipple | Observational (12) | 129 | Cessation of menses | Observational (12, 15) | 12 |
| | Softened skin | Observational (12) | 129 | Hirsutism | Observational (12) | 28 |
| | Reduced testicular volume | Observational (28) | 28 | Clitoral growth, average 4–5 cm | Observational (15) | 13 |
| | Decreased spontaneous erections | Observational (15) | 60 | Laryngeal prominence | Observational (10) | 85 |
| | Decreased libido | Observational (12) | [a] | Increased libido | Observational (10) | 85 |
| | Redistribution of fat | Observational (10) | 300 | Breast atrophy, histological | Observational (36) | 12 |
| | Calming effect | Observational (10) | 300 | Redistribution of fat | Statistical change (37) | 15 |
| | Testosterone to female levels | Statistical change (29) | 14 | Testosterone to male levels | Statistical change (38) | 18 |
| | Decreased hair growth | Statistical change (30) | 21 | Increased muscle mass | Statistical change (38) | 10 |
| Negative effects | Venous thrombosis | Observational (6) | 813 | Acne | Observational (6) | 293 |
| | Cholelithiasis | Observational (6) | 813 | Weight increase >10% | Observational (20) | 122 |
| | Hyperprolactinemia | Observational (6) | 813 | Elevated liver enzymes | Observational (6) | 293 |
| | Elevated liver enzymes | Observational (6) | 813 | Increased hematocrit | Observational (13) | 42 |
| | Depression | Observational (20) | 303 | endometrial hyperplasia | Observational (39) | 19 |
| | Decrease in hemoglobin | Observational (13) | 46 | Sleep apnea | Observational (40) | [a] |
| | Prolactinoma | Case reports (8, 26, 31) | 3 | Aggression and hypersexuality | Observational (10) | 85 |
| | Breast cancer | Case reports (32) | 3 | Poor lipid profile | Statistical change (41) | 29 |
| | Prostatic carcinoma after orchiectomy | Case report (33) | 1 | Decreased insulin sensitivity | Statistical change (34) | 13 |
| | Decreased insulin sensitivity | Statistical change (34) | 18 | Increased IGF | Statistical change (35) | 35 |
| | Decreased IGF | Statistical change (35) | 56 | Decreased bone mineral density after gonadectomy | Statistical change (16) | 32 |
| | | | | Ovarian cancer | Case report (42) | 2 |

[a] Not reported.

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| | Male to female | Female to male |
|---|---|---|
| Treatment | Ethinyl estradiol 100 μg/d or conjugated equine estrogen 2.5 mg/d.<br>Transdermal once >40 yr old. Adjust to suppress total testosterone to <25 ng/dl. If estrogen doses reach twice above recommendations, add spironolactone, cyproterone acetate, or GnRH agonists to minimize estrogen requirement. | Testosterone esters 200 mg im every other week or transdermal testosterone 5 g/d to obtain serum testosterone in the mid-male range. |
| Initial visit | PSA as per standard recommendations<br>Lipid profile<br>Liver function tests | Weight<br>Lipid profile<br>Glucose levels |
| Every 3–6 months | Testosterone levels until stable<br>Estradiol blood level (compliance)<br>Liver function tests<br>Lipid profile<br>Encourage breast exams | Lipid profiles<br>Complete blood count to rule out polycythemia<br>Testosterone levels<br>Liver function tests |
| Every 6 months to 1 yr pre-operative | Visual fields to assess for prolactinoma<br>Serum prolactin<br>Liver profile<br>Over 50 yr: PSA, consider mammogram | Pelvic exam with Pap smears as per standard protocol<br>Endometrial ultrasounds (every 2 yr) |
| Every 6 months to 1 yr post-operative | Decrease estrogens to HRT doses<br>Dexa scan to assess osteoporosis | Decrease testosterone: titrate to maintain serum testosterone 500 μg/dl (17.35 SI).<br>Dexa scan |

HRT in postmenopausal women, conjugated equine estrogens 0.625 mg/d, transdermal ethinyl estradiol 0.05–0.1 mg/d, or ethinyl estradiol 0.02–0.05 mg/d. PSA, prostate-specific antigen.

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# Monitoring of Transmen

- 1. Evaluate patient every 2–3 months in the first year and then 1–2 times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
- 2. Measure serum testosterone every 2–3 months until levels are in the normal physiologic male range:*
- a. For testosterone enanthate/cypionate injections, the testosterone level should be measured mid-way between injections. If the level is >700 ng/dl (24.3nmol/l) or <350 ng/d (12.1 nmol/l)l, adjust dose accordingly.
- b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection.
- c. For transdermal testosterone, the testosterone level can be measured at any time after 1 week.
- d. For oral testosterone undecanoate, the testosterone level should be measured 3–5 hours after ingestion.
- e. Note: During the first 3–9 months of testosterone treatment, total testosterone levels may be high although free testosterone levels are normal due to high sex hormone binding globulin levels in some biological women.

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# Monitoring Transwomen

- 1. Evaluate patient every 2–3 months in the first year and then 1–2 times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
- 2. Measure serum testosterone and estradiol every 3 months.
- a. Serum testosterone levels should be <55 ng/dl. **(1.91 nmol/l)**
- b. Serum estradiol should not exceed the peak physiologic range for young healthy females, with ideal levels, 200 pg/ml **(734 pmol/l)**
- c. Doses of estrogen should be adjusted according to the serum levels of estradiol.
- 3. For individuals on spironolactone, serum electrolytes particularly potassium should be monitored every 2–3 months initially in the first year.
- 4. Routine cancer screening recommended in non-transsexual individuals (breasts, colon, prostate).
- 5. Consider BMD testing at baseline if risk factors for osteoporotic fracture are present (e.g., previous fracture, family history, glucocorticoid use, prolonged hypogonadism).
- In individuals at low risk, screening for osteoporosis should be conducted at age 60 or in those who are not compliant with hormone therapy

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# Monitoring of Transmen

- 1. Evaluate patient every 2–3 months in the first year and then 1–2 times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
- 2. Measure serum testosterone every 2–3 months until levels are in the normal physiologic male range:*
- a. For testosterone enanthate/cypionate injections, the testosterone level should be measured mid-way between injections. If the level is >700 ng/dl (24.3nmol/l) or <350 ng/d (12.1 nmol/l)l, adjust dose accordingly.
- b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection.
- c. For transdermal testosterone, the testosterone level can be measured at any time after 1 week.
- d. For oral testosterone undecanoate, the testosterone level should be measured 3–5 hours after ingestion.
- e. Note: During the first 3–9 months of testosterone treatment, total testosterone levels may be high although free testosterone levels are normal due to high sex hormone binding globulin levels in some biological women.

# Monitoring of Transmen

- 3. Measure estradiol levels during the first 6 months of testosterone treatment or until there has been no uterine bleeding for 6 months. Estradiol levels should be <50 pg/ml (183 pmol/l)
- 4. Measure CBC and liver function tests at baseline and every 3 months for the first year and then 1–2 times a year. Monitorweight, blood pressure, lipids, fasting blood sugar (if family history of diabetes) and hemoglobin A1c (if diabetic) at regular visits.
- 5. Consider BMD testing at baseline if risk factors for osteoporotic fracture are present (e.g., previous fracture, family history, glucocorticoid use, prolonged hypogonadism).
- In individuals at low risk, screening for osteoporosis should be conducted at age 60 or in those who are not compliant with hormone therapy.
- 6. If cervical tissue is present, an annual pap smear is recommended by the American College of Obstetricians and Gynecologists.
- 7. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society

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# Minor side effects

| Side -Effect | Current (n=83) | Current (%) | Historical (n=98) | Historical (%) |
|---|---|---|---|---|
| Low mood | 1 | 1.2% | 1 | 1.0% |
| Tiredness | 3 | 3.6% | 3 | 3.1% |
| Low libido | 1 | 1.2% | 4 | 4.1% |
| Sweating | 1 | 1.2% | 1 | 1.0% |
| Weight loss | 2 | 2.4% | 0 | 0.0% |
| Breast tenderness | 1 | 1.2% | 0 | 0.0% |
| Insomnia | 1 | 1.2% | 0 | 0.0% |
| Hypercholesterolaemia | 4 | 4.8% | 3 | 3.1% |
| Mood swings | 3 | 3.6% | 0 | 0.0% |
| Pruritis | 3 | 1.2% | 0 | 0.0& |
| Headaches | 1 | 1.2% | 5 | 5.0% |
| Anxiety | 0 | 0.0% | 1 | 1.0% |
| Dizziness | 0 | 0.0% | 1 | 1.0% |
| Blurred vision | 0 | 0.0% | 1 | 1.0% |
| Nausea | 0 | 0.0% | 1 | 1.0% |
| Brittle nails | 0 | 0.0% | 1 | 1.0% |
| Drowsiness | 0 | 0.0% | 1 | 1.0% |
| Intermittent claudication | 0 | 0.0% | 1 | 1.0% |

# Actions of Oestrogen

- ↓ Total cholesterol
- ↑HDL
- ↓LDL
- ↑ Triglycerides
- ↓ Fasting glucose and insulin
- ↑ Fibrinogen
- ↑Endothelial function

# Effect of Testosterone in Transmen

- Increased facial and body hair
- Male pattern baldness
- Voice change
- Increased libido
- Increased social drive and arousability
- Cliteromegally
- Increased muscular strength
- Redistribution and decrease of body fat
- Breast atrophy