Oestrogen, progestogens and assessing risks of hormones

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My interest

- Minimal exposure during training
- "Unmet need" within endocrinology (private/public)
- Interesting endocrinology
- Interesting patient population

Our role

- Important in improving mental health outcomes
  - Reduced gender dysphoria
  - Reduced anxiety & depression
  - Reduced perceived stress
  - Improved QOL
- Lower access to health care
  - Our stigma
  - Endocrinologist:
    - 20% “very comfortable” with gender identity
    - 40% “somewhat” or “very competent” to Rx
  - Rx
    - 70% Rx but 40% consistent
    - 50% not prescribed
      - Lack of consistency
      - Lack of monitoring

Aims of treatment

- Reduction in gender dysphoria
- Suppress endogenous testosterone production/action
- Induce female secondary sexual characteristics – breast formation & female fat distribution
- Maintain hormone levels within the normal physiological range
  - Need to continue oestrogen replacement after GRS
  - Supraphysiological levels of hormones not required

Feminising hormone regimes

- Oestrogen
  - Alone will suppress gonadotropin output and hence androgens
    - Reduces testosterone to low-normal male range (6.9-10.4nmol/L) but still above female range
  - Induce female sexual characteristics
- Anti-androgen
  - Suppresses androgen production & reduces the doses of oestrogen required
- (progesterone)

Types of oestrogen replacement

- Agents
  - Conjugated/synthetic oestrogens
    - Cannot measure serum levels
  - 17 β-oestradiol

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    - Cannot measure serum levels
  - 17 β-oestradiol
- Route
  - Transdermal
  - Oral
  - Buccal or parenteral

Type of oestrogen replacement

- Lower risk of VTE in TD and bypass of 1st pass metabolism (Goodman *et al)*
  - Less effect on hepatic protein synthesis including steroid-biding proteins and marks fro inflammation, coagulation and fibrinolysis
  - One study showed no cases of VTE in 162 MTF treated with TD oestrogen over 5 years
- VTE in MTF patients on oral oestrogen (Arnold *et al)*
  - 1286 patient years (mean 1.9/pt)
  - Only 1 patient sustained a VTE – incidence 7.8/10 000 pt years
- 20-fold increase risk of VTE in Dutch TG population
  - But used synthetic oestrogens – inability to monitor & oral
- SR in JCEM 2015
  - 15 observational studies
  - PO vs TD
    - First episode of VTE – RR 1.63 (CI 1.40-1.90)
    - DVT – RR 2.09 (CI 1.35-3.23)
    - Stroke – RR 1.24 (CI 1.03-1.48)
    - But not MI – RR 1.17 (CI 0.80-1.71)

Type of oestrogen replacement

- Consider TD if
  - Other risk factors for VTE present
    - Cigarette smoking
    - >40yo
    - FHx or PHx of VTE
    - Obesity
    - Recurrent immobility (ie travel, work)
- Minimising the risk for VTE
  - Smoking cessation
  - Weight reduction
  - Thrombophilia testing if PHx/FHx VTE
  - Consider ceasing prior to surgery (3-4 weeks prior, restart when mobilising)

Contraindications to oestrogen

- Prior VTE + underlying coagulopathy
  - Still can consider transdermal oestrogen
- Oestrogen-sensitive malignancy
- Relative
  - End-stage liver disease
  - Cardiovascular disease/cerebrovascular disease
  - Severe migraine
  - History of breast cancer

Doses of oestrogen

- Oral oestradiol
  - 2-6mg/d
- Transdermal oestradiol
  - 100-400ug patch
- Aim to keep the oestradiol in the normal premenopausal range (average ~400)
- My preference is to start relatively low and gradually increase

Anti-androgens

- Spironolactone
  - Mineralocorticoid receptor antagonists
  - Also competitive inhibitor of the AR, 5^{α}-reductase inhibitor, inhibits testicular steroidogenesis
  - -> Inhibits testosterone secretion & androgen binding to the receptor
  - Baseline testosterone not predictive of response
  - Liang JJ *et al* – effect on serum testosterone
    - Nine months to achieve steady state testosterone levels
    - Pts with normal BMI > testosterone than obese
    - Highest suppressing quartile = testosterone mean 0.35nmol/L (max 0.94nmol/L)
      - Aim is <1.73nmol/L
    - Second highest suppressing quartile – below normal male range (mean 3.47nmol/L)
    - One quartile not able to achieve significant suppression

Anti-androgens

- Cyproterone acetate
  - Progestin (suppresses gonadotropins) & AR antagonist
  - Gava *et al*
    - CPA vs leuprolide with transdermal oestradiol in MTF patients
      - LH, FSH and total testosterone declined by 3/12, nadir at 12/12
      - Prolactin increased in CPA group only
      - Bone metabolism and DEXA no change (inc PTH in Leu)
      - Leu: increased TC & HDL, CPA: reduced HDL
      - No major adverse effects or change in psychological well-being
  - Theoretical risks:
    - Depression
    - Multiple meningiomas has been reported with longer-term use of CPA (>25mg/d)
    - Hepatotoxicity at high doses
    - Suppression of the HPA axis

Anti-androgens

- (GnRH agonists) – not widely used, costly
- Other progestins
  - MPA – can suppress gonadotrophin production
  - Less effective than other agents
  - Mean testosterone 5.9 vs 3 with spironolactone

Doses of anti-androgen

- Spironolactone 100-200mg/d
- Cyproterone acetate 50-100mg/d
- Comparison of agents
  - MTF (Fung *et al*)
    - Spironolactone increases HDL (by 0.1mmol/L) & CPA reduced (by 0.07mmol/L)
    - CPA larger increase in prolactin (+ 64 vs + 251mIU/L)
    - Serum testosterone – CPA 0.8nmol/L vs spironolactone 2.0nmol/L
    - Increased urea with spironolactone
  - Non-TG population
    - TC & HDL higher in cyproterone
    - Androstenedione reduced in spironolactone
    - Similar effects on hyperandrogenism (in PCOS)

Feminising effects of Rx

Effect	Onset	Maximum
Redistribution of body fat	3-6 months	2-3 years
↓ muscle mass & strength	3-6 months	1-2 years
Softening skin, ↓ oiliness	3-6 months	
↓ libido	1-3 months	3-6 months
↓ spontaneous erections	1-3 months	3-6 months
Male sexual dysfunction	Variable	Variable
Breast growth	3-6 months	2-3 years
↓ testicular volume	3-6 months	2-3 years
↓ sperm production	-	>3 years
↓ terminal hair growth	6-12 months	>3 years
Scalp hair	No regrowth	
Voice changes	Nil	

Progesterone?

- Progestins
  - Role in mammary development on a cellular level
  - No clear evidence of benefit – no clear enhancement of breast growth or reduction in testosterone levels
  - Risks – weight gain, lipids, mood
  - ? Role in breast CA & CVD
  - Micronised progesterone may have better tolerance & less lipid effect than MPA

Side effects of treatment

- VTE (discussed)
- Gallstones
- Elevated liver enzymes
- Weight gain
- Hypertriglyceridaemia
- Increased prolactin
- Increased blood pressure

Complications – hormonal

1. Hyperprolactinaemia
   - Oestrogen can + pituitary lactotrophs
     - Cases of prolactinomas years after oestrogen Rx
       - Up to 20% will have a rise in prolactin with a enlargement of the pituitary
       - Normalises on dose reduction
       - MRI if significant rise or no improvement with dose reduction
   - Reversible increase seen with CPA (Defreyne *et al)*
     - Increase to mean ~ 504mIU/L vs 190mIU/L (baseline)
     - Normalised after orchidectomy or cessation of Rx
     - (? More from CPA than the oestradiol)
   - Nota *et al*
     - 196% increase in prolactin within 1yr after Rx CPA and oestradiol
     - 30% hyperprolactinaemia
     - Normalised after gonadectomy
   - (Decrease in PRL of 25% in FTM)
   - Measure at baseline, yearly for 1st 2 years then every 2yrs

Complications – hormonal

2. Bone density
   - Oestradiol correlates more with bone density in genetic males
   - Oestradiol is more important for peak bone mass
   - Oestrogen preserves BMD in MTF pts
   - Some risk if non-compliance or post-operatively
   - Wiepjes *et al*
     - MTF: (CPA and estradiol) – 1yr
       - Increase in LS density of 3.67% and FN (1.86%)
     - FTM
       - TO increased by 1.04%, no change in FN, LS increased (4.32 if >50yo, 0.68 if <50yo)
       - Probably from aromatisation of testosterone to oeastradiol

Complications – malignancy

1. Breast cancer
   - Limited data
   - Dutch cohort (1800 MTF) mean 15yrs only 1 case
   - WHI showed no increase risk for women on oestrogen alone (without progesterone) for 7 years
   - Women with primary hypogonadism on oestrogen have a lower risk of breast cancer
   - -> oestrogen unlikely to increase the risk of breast cancer in the short-term (<20-30 yrs)
   - If using progesterone probably higher risk
   - Often continued after usual menopausal age
   - Screening
     - Regular examination
     - Annual mammogram if oestrogen for >30 years or from 50yo if additional RF:
       - Oestrogen & progesterone >5yrs
       - BMI >35
       - FHx

Complications – malignancy

1. Prostate
   - Usually not removed during surgery
   - Very rare – androgen deprivation therapy
   - No clear evidence that oestrogen induces hypertrophy or dysplastic changes in the prostate
   - Deebel *et al* (2017)
     - 10 cases published in MTF patients
     - ? Role of androgens in development of CaP, oestrogen may not be protective
     - Impact of bilateral orchidectomy is unclear
   - 1 case report suggested role for oestrogen in pathogenesis of CaP (20yrs Rx) (Sharif *et al)*
     - IHC showed ER-α staining in stromal cells
   - Regular PSA & DRE as per genetic male population

Complications – misc

1. Cardiovascular disease
   - Systematic review (JCEM) Maraka *et al*
     - MTF (oral oestrogen): increase in TG at ≥ 24/12 (0.36mmol/L)
     - FTM: increase in TG (0.24mmol/L), increase LDL (0.44), decrease HDL (0.23)
     - Few clinical outcomes (MI/CVA/VTE/death)
   - Largest cohort of MTF pts followed for 10 yrs showed no increase in CV mortality (32% cig smokers)
   - No clear evidence of the effect of oestrogen
   - Generally normalises after gonadectomy
2. Hormones post gonadectomy
   - Cease anti-androgen (can consider low dose for hair production)
   - Reduce dose of oestrogen

Older TG population

Mahan *et al*

- 70% transgender adults aged >65 delayed transition to avoid discrimination
- Aim for age-appropriate oestradiol levels
- Chronic disease states eg CVD & osteoporosis are more common
- Higher risk of VTE – consider TD
- CVD
  - Risk of worsening cardiac outcomes esp if history of CVD
  - Also may increase risk of hyperTG, weight gain, elevated LFTs, T2DM & HTN
  - Oestrogen can increase the risk of VTE if >40 and other risk factors
  - Can consider ASA
- Osteoporosis
- Risk of hyperK with renal impairment & spironolactone

Before starting therapy

- Diagnosis of gender dysphoria
  - Current mental state
  - Ideal to have psychiatric/psychology input
- Patient's expectations of therapy
  - Goals – androgynous/feminisation
  - Limitations of hormone therapy
- Capacity
- Risks assessment for oestrogen replacement
  - Consideration of route of replacement
- Fertility
- Baseline bloods - FSH, LH, oestradiol, testosterone, PSA, prolactin, E/LFTs, lipids, FBC

Summary of agents

- Oestrogen
  - Oestradiol (patch) 50ug starting then increase to 75-100ug at 3/12
  - Oestradiol (oral) 1mg starting then increase to 2mg at 3/12
  - Titrate to serum oestradiol
  - PO vs TD based on risk factors for VTE
  - Consider more gradual dose escalation if older, significant hypertension, baseline LFT abnormality
- Anti-androgen
  - Spironolactone 25-50mg BD starting dose
  - Titrate CPA to serum testosterone
  - Consider lower dose if renal impairment, other anti-hypertensives or baseline low testosterone

Monitoring

- Frequency of visits
  - 3/12 during the first year
  - 6-12/12 thereafter
- Mental state
- Physical changes – breasts, weight
- Biochemistry
  - FBC, E/LFTs (K, liver function), oestrogen, LH, FSH, testosterone, lipids (TG)
  - PSA & breast screening
  - Prolactin
  - Consider lipids
  - Bone density
    - Baseline if previous fracture, FHx, prolonged hypogonadism

Fertility

- Low rates of fertility preservation in adolescents (post-pubertal)
  - 73 pts – 72 documented discussions
  - 2 attempted fertility preservation
  - 45% desire to adopt
  - 21% no children

When to refer

- Significant medical comorbidities
  - Major organ impairment
- Conditions likely to be worsened by hormonal therapy
  - Hypertension
  - Diabetes (esp T1DM)
  - Prolactinomas
- Multiple risk factors for VTE/CVD
- Fertility induction/preservation

Conclusion

Most importantly, as health care providers we should provide support and act as advocates for our transgender patients

Thank you

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Fertility

- Hypospermatogenesis → azoospermia
- Consider sperm banking
- hCG most commonly used +/- FSH
  - After hCG
    - 50% ↑ testicular volumes after 6-18mts
    - 80% spermatogenesis
  - hCG + clomiphene/tamoxifen/anastrozole/FSH
    - 95% return or improved sperm counts
- In HH patients Rx hCG & FSH for 6/12
  - Testosterone increased in 98%
  - 80 positive sperm count (median 5/12)