



# Patients with Sexual Problems Treated with Hormonal Treatments

AAMS Seminar

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# Ageing and Sexual Problems

## Overview

The gradual decline in sexual function with age and the onset of sexual symptoms are a consequence of specific physiological changes.

Some of these changes are limited or reversed by the judicious use of sex hormones and careful attention to health and lifestyle factors.

# Physiological Changes in Men

## Hypophysial-pituitary axis

Hypothalamus (Arcuate nucleus):



Gonadotrophic Releasing Hormone (GnRH)

Ant. Pituitary:



LH, FSH, Prolactin

Testes:

Leydig cells produce testosterone

Sertoli cells activate spermatogenesis

# Physiological Changes: in Men

## Penis:

sensation ↓; erection less firm; arousal may require direct stimulation; refractory period increased; suspensory ligament lengthens (increasing 'angle of dangle').

## Ejaculation:

greater stimulation and time to achieve ejaculation;  
↓ volume of ejaculate

## Prostate:

↓ prostatic fluid, increased stromal tissue may cause obstructive urinary symptoms

## Testes:

↓ size; impaired response to FSH and LH; ↓ sperm production; ↓ T

# Physiological Changes: in Men

## **Testicular Function:**

Sertoli Cells: Sperm count ~ normal,  
↓ Sperm motility; abnormal forms.

Seminiferous tubules: degenerative  
changes; ↓inhibin production.

(leads to failure of feed-back loop  
suppressing FSH production by pituitary).

- above suggests end organ failure

# Physiological Changes: in Men

## **Testicular Function:**

Leydig cells:

↓ number, abnormal forms

↓ testosterone production (despite  $<$  LH levels).

hCG stimulation test show reduced Leydig cell response.

- above suggests end organ failure

# Physiological Changes: in Men

## **Pituitary Function:**

↓ Amplitude of LH secretory bursts, but giving (hypothalamic) GnRH restores LH secretory response, suggesting impairment at hypothalamic level while the pituitary retains its function.

# Clinical Symptoms: in Men

## Symptoms of Late Onset Hypogonadism (LOH)/Andropause:

∇ ↓ Libido

- Erectile impairment with loss of spontaneous (nocturnal) erections
- Night sweats and hot flushes
- Aching and stiff joints
- Irritability



# Hormonal Influences on Ageing Hypophysial-pituitary axis in Women

Hypothalamus (Arcuate nucleus):



Gonadotrophic Releasing Hormone (GRH)

Ant. Pituitary:



LH, FSH, Prolactin

Ovary: E2, Estriole, Estrone, DHEA, T

# Physiological Changes: Women

Estrogen deficiency leads to:

- Vagina: tissue thins and length contracts
  - ↓ lubrication and slower lubrication
  - ↓ contractions during orgasm
- Uterus and cervix: smaller
  - ↓ contractions during orgasm
- Labia and clitoris: ↓ engorgement during arousal
- Orgasm: ↓ intensity and duration
- Sex drive: In part androgen > estrogen dependent.

# Clinical Symptoms: Women

E2 dependent, reversible after menopause:

- Vasomotor instability: night sweats, hot flushes
- Genital atrophy: vaginal dryness, discomfort on SI
- Bladder irritability: frequency, stress incontinence
- Cognitive impairment, ↓ short-term memory and reduced well-being

# Menopause v. Andropause/LOH

In men and women sexual changes occur with age that are associated with hormonal depletion:

Women at menopause have  $\downarrow$  E2,  $\uparrow$  FSH/LH with loss of menstrual cycle (and cessation of ovulation) occurring as a discrete event.  $\downarrow$  Libido (T dependent).

Men at andropause have  $\downarrow$  T,  $\uparrow$  FSH/LH  $\downarrow$  libido and  $\downarrow$  fertility gradually over time.

How significant in male hormone depletion are confounding variables: stress, non-endocrine illness, malnutrition, obesity and drugs/medication?

# Male Hormone Therapy



# Diagnostic Criteria of Andropause/LOH

Biochemical Diagnosis:

Total Testosterone (TT)  $< 12 \text{ nmol/L}$  ( $346 \text{ ng/dL}$ )

Free Testosterone Index (TT/SHBG) ( $49-169\%$ )

Or

Free Testosterone  $< 250 \text{ pmol/L}$  ( $72 \text{ pg/mL}$ )

NB: Blood samples taken before 11.00am (to obtain peak levels and consistent results).

Reference ranges may vary between labs.

# Associated Clinical Conditions

Sexual activity is a function of good health generally. While assessing HT consider

Physical factors:

- CVD, DM and Cancer (testosterone directly or indirectly may affect the progression of these conditions).

Psychological factors:

- Previous mental health eg depression, and present relationship

# Actions of Androgens in Clinical Disease:

## Prostate Cancer

- Androgen (DHT) receptors are widespread in the prostate.
- Alpha-reductase converts T to the more stable DHT.
- T produces slight prostate enlargement and increased PSA in hypogonadal patients.  
Douglas 1995
- There was no evidence that T caused prostate cancer during 3 year FU. Nomura 1998
- T replacement decreased PSA levels.
- E2 opposes T effects on prostate. Coffey 1987



# Androgens and Sexual Function in hypogonadal men

Androgens regulate sexual function with central and peripheral effects:

Centrally:

∇ ↑ libido (interest and motivation) Alexander 1999

Peripherally:

- Activates nitric oxide synthase which regulates activity in cavernosal smooth muscle to promote erection Lugg 1996

# Androgens and Sexual Function in (young) hypogonadal men

T replacement increases:

- Sexual activities
- Sexual daydreams, thoughts and desire
- Spontaneous and nocturnal erections

Alexander 1999

- Penile rigidity
- Penile sensitivity

Lugg 1996

Orgasm and ejaculation are androgen dependent

Bhasin 1988

# Androgens: Other Actions

T has systemic actions other than on sexual function to:

- Maintain muscle strength and mass Melton 2000
- Reduce adipose tissue Tenover 1998
- Maintain Bone Density Tenover 1998
- Act on neurones and neuro-transmitters with effects on verbal fluency, memory and energy Alexander 1999

These provide benefits to health and QOL, which are unrelated to sexual function directly, none the less benefit it indirectly.

# Hormone Therapy

## Assessment:

### Blood tests:

- Hormones: Total testosterone
- Sex Hormone Binding Globulin (SHBG)
- Free Testosterone Index (FTI)
- Dehydrotestosterone (DHT)
- Dihydroepiandrosterone (DHEA)
- Oestradiol (E2)
- Luteinising Hormone (LH)
- Follicle stimulating Hormone (FSH)
- Prolactin.

# Hormone Therapy

## Assessment

Other Blood Tests: Full Blood Count (FBC) and Liver Function Tests (LFTs)

- Bone Density: Dexascan
- Assess Prostate Function: ? Family History, current urinary symptoms, DRE, prostate specific antigen (PSA)
- If in doubt do rectal u/s.

With Erectile Dysfunction present:

Lipids, blood sugar and cardiovascular function  
should be assessed

# HT Assessment

Some Drugs may interfere with T metabolism

- Alcohol: Promotes T conversion to E2; damages Leydig cells (↓ sperm production)
- Aminoglutethamide, Ketoconazole: inhibit steroidogenesis and reduce T levels.
- Cimetidine, spironolactone, cyproterone acetate: androgen receptor antagonists
- Saw Palmetto, finasteride: 5-alpha-reductase inhibitors inhibit DHT production (decrease libido and produce ED).

# HT Assessment

## Drugs that interfere with SHBG:

- Barbiturates, anticonvulsants: Hepatic enzyme induction increases SHBG reducing urinary clearance of T and FT, and producing symptoms of andropause.
- Danazol lowers hepatic synthesis of SHBG and displaces T from binding sites on SHBG. Produces increased FT levels and counters andropause symptoms.

Curruthers 2000



# Treating with Testosterone:

In general:

Short-acting natural testosterone to be preferred

Therapeutic Goal of treatment is the mid-range level of young adult male

(TT about 20nmol/L or SHBG/TT ratio >60)

\*ISSAM

\*International Society for the Study of the Aging Male

# Treating with Testosterone

- Orally: Testosterone undecanoate (Restandol): 80mg twice daily; Natural testosterone 100mg/d
- Transdermal Patch: Testosterone (Andropatch) 5mg/d
- I/m testosterone as propionate 30mg, phenylpropionate 60mg, isocaproate 60mg, decanoate 100mg (Sustanon): 250mg every two/three weeks
- I/m testosterone undecanoate (Nebido) 1000mg every 3 months
- Cream/gel: Testosterone (Androgel); DHT (Andractim)
- Implant: Testosterone <600mg every 3 months.

# Review of benefits from HT

Meta-analysis of male HRT showed testosterone administration is associated with greater improvement in sexual function compared to placebo treatment in men with sexual dysfunction and low testosterone levels.

Jain 2000

Testosterone may also favorably affect partner interactions and intimacy due to an overall increase in sexual desire and sense of well-being, independent of the change in erectile function.

Bhasin 2001

# Be selective in choosing who to treat!

‘The decision to institute testosterone replacement in older men with low testosterone levels must be individualised and accompanied by a detailed discussion of the potential risks and benefits.’

Bhasin 2001

# Hormone Therapy

## HCG (Human Chorionic Gonadotrophin)

Rationale for use:

Promoting the bodies' production of testosterone with HCG is physiological whereas replacement of testosterone exogenously suppresses endogenous production.

# Hormone Therapy

## HCG (Human Chorionic Gonadotrophin)

- Indication: In 'the young old' with partial androgen deficiency and a low FSH.
- Derived human placenta has FSH-like action.
- Stimulates Sertoli cells and sperm production
- Increases Testosterone and FTI
- Increases morning erections
- Improves skin texture
- Dose: 1250iu s/c twice weekly

# Hormone Replacement Therapy

## HCG (Human Chorionic Gonadotrophin)

625 men with ADAM, aged 40-87, in a 2.5 year study showed increased T with hCG administration.

Patients showed increase in T by <250%, with improvement to physical and mental health, improved memory, libido and potency. Lipid profiles improved and bone turnover showed increased osteoblastic activity and decreased urinary Ca excretion

Gomula, Kalintchenko 2002

# Erectile Dysfunction

## Definition:

‘A persistent inability to attain and maintain an adequate erection to permit satisfactory sexual performance’.

NIHCS, 1992



# Erectile Dysfunction (ED)

## Pathogenesis

- Physical factors primary cause in 75% of cases. (heart disease, hypertension, DM, and medication)
- Psychological factors predominate in 25% (anger, depression and relationship issues)
- A psychological reaction of anxiety and avoidant behaviour is a common reaction to established ED
- Life-style factors (stress, cigarette smoking and obesity) also correlate with ED

Feldman, 1994

# Erectile Dysfunction (ED)

Prevalence:

In a random sample of 1290 men:

- Total ED increased from 5-15% between the ages of 40 and 70.
- Some degree of ED occurred in 52%
- In DM prevalence 15% at 30, < 55% aged 60

Feldman, 1994

Massachusetts Male Aging Study (MMAS)

# Hormonal Aid to Arousal

Testosterone restores erectile response in 40-60% of hypogonadal patients

Mulhall, 2004

# Combined Hormonal/PDE5 or Prostaglandin E1 Therapy

In ED with LOH the best treatment is currently a PDE5 inhibitor (eg Sildenafil, Vardenafil, Tadalafil) or Prostaglandin E1 (eg Caverject) plus Testosterone.

# Follow-up of patients receiving HT

- PSA and DRE at 3, 6, 9,12 months and then annually.
- Transrectal U/S with biopsy only if above abnormal
- Hb and hematocrit at 3, 6, 9,12 months and then annually.
- Bone density (dexascan) may be advisable 2 yearly
- Prostate cancer is not a total bar to later treatment with testosterone following its successful treatment.

\*ISSAM, 2004

\*International Society for the Study of the Aging Male

# Hormone Therapy (HT): Dehydroepiandrosterone (DHEA)

## Rationale for Use

- Normal Range 0.95 -11.6 micromol/L (women)  
2.20 -15.2micromol/L (men)
- Levels are reduced 50% between age 25 and 55

# Hormone Therapy (HT)

## Dehydroepiandrosterone (DHEA)

### Rationale for Use

Study: double-blind cross-over study

Age: 40-70 years (men and women)

Treated: DHEA 50mg

### Results:

- improve energy and well-being
- sleep and ability to handle stress

Morales, 1994

# Hormone Therapy (HT)

## Dehydroepiandrosterone (DHEA)

### Rationale for Use

Study: 280 men and women

Age: 70+ years

Treated: DHEA 50mg for 1 year

### Results

Women only showed:

↑ libido, sexual fantasies, activity and satisfaction



# Hormone Therapy (HT)

## Dehydroepiandrosterone (DHEA)

Treatment

Recommended dose:

Men: Oral 50-100mg  
s/l 25mg (women)

Women: oral 10-25mg  
s/l 5-15mg

Side-effects: Changes to pattern of hair growth.

NB: monitor levels of testosterone and IGF-1

# Hormone Therapy in Women (HT)

## Predictors of HT use:

- Socio-economic status: Higher status associated greater use.
- Age: Early menopause
- Type: Surgery associated HT 3 times more often

# Hormone Therapy (HT) for Women: Oestrogens

## Investigations:

E2

LH, FSH,

TT, SHBG, FTI

DHEA(S)

TSH

Lipids, LFT's

# Hormone Therapy (HT) for Women: Oestrogens

## Minimum dose to maintain bone density:

- Conjugated equine oestrogens 0.625 mg (Premarin)
- Oestrogen sulphate 1.5mg (Harmogen)
- Oestradiol 17 $\beta$  as:
  - Oral (Progynova, Climaval) 1-2mg
  - Transdermal (Progynova TS) 0.05mg
  - Implant 6 monthly 50mg

# Hormone Therapy (HT) for Women: Oestrogens

## Side-effects:

- Mastalgia (painful breasts)
- Bloating
- Bleeding
- 'Premenstrual Tension'
- Depression

# Hormone Therapy (HT) for Women: Oestrogens

## Endometrial Cancer:

- 'Unopposed' oestrogens increase the risk; progesterone protects against it:
- Sequential combined (Cyclical) therapy: Progesterone is given for 12 days per month and is followed by withdrawal bleeding
- Continuous combined therapy: Progesterone is given continuously; there may be spotting/unpredictable bleeds (resolves in < 9 months); usually only given 1yr after menopause

# Hormone Therapy (HT) for Women: Oestrogens

## Weigh up risks and Benefits

**Breast Cancer Risk** (Prevalence per 10,000 women):

- No oestrogens/oestrogens or HT for less than 2 years is 45/10,000 women
- E2 for 5 years is 47
- E2 for 10 years is 52
- E2 for 15 years is 57

The risk of breast cancer continues into the 7th decade and later. Continue doing mammograms late.

Increased risk if FH of breast cancer. Check genetic status.

# Hormone Therapy (HT) for Women: Progestogens

## Minimum dose for endometrial protection:

For 12 days per month:

- Norgestrel (Neogest) 0.15mg
- Norethisterone (Micronor) 1mg
- Medroxyprogesterone (Provera)# 10mg
- Dydrogesterone (Duphaston) 10mg
- Micronised progesterone 200mg

# For continuous therapy dose of Medroxyprogesterone is 2.5mg



# Hormone Therapy (HT) for Women

## Risks re-evaluated: HERS study

Mean age 67 years

High dose HT

Showed women with established IHD on high dose HT will be at high risk of thrombotic event in the first year .

Post menopausal women should not be put on HT to reduce CV risk.

Previous thrombo-embolic disease contraindicates HT

# Hormone Therapy (HT) for Women

## Risks re-evaluated

After 5 years of combined HT (Oestrogen and progestogen) for every 10,000 women there will be:

- ↑ Deep Vein Thrombosis: 4 extra cases in women over 50
- ↑ Ovarian cancer: 4 extra cases
- ∇↑ Strokes: 1 extra case aged 50-59 years  
4 extra cases for women 60+ years
- ∇↑ Breast cancer: 2-6 extra cases

Wisdom; Women's Health Initiative; The Million Women Study, Oxford Univesity

# Hormone Therapy (HT) for Women

## Risks re-evaluated

WHI non-HRT randomised arm:

Treatment with Calcium, Vitamin D and a low fat diet  
did not reduce the incidence of:

Osteoporosis,  
Ca breast, colon/rectum,  
CVD

# Hormone Therapy (HT) for Women

## Risks re-evaluated

### Non-conventional HT

With bio-identical hormones (in doses that maintain physiological hormone levels) the risk levels for breast and uterine cancer and DVT found with conventional forms of HT are not applicable

# Hypoactive Sexual Desire Disorder

## Definition

Impairment of sexual interest, thoughts and fantasies, and a lack of responsive desire;

Motivation to becoming sexually aroused is reduced;

Lack of interest (in sex) is greater than that accounted for by ageing alone or the lengthening of a relationship.

# Hypoactive Sexual Desire Disorder

The symptom of low sexual desire is only a disorder when an individual feels it to be distressful.

The consequent effects on a relationship may also motivate requests for treatment.

Dennerstein, 2006

# Hypoactive Sexual Desire Disorder

## Prevalence:

Age 20-49: 16% [7%\*]; 29% [16%\*] with surgical menopause.

Age 50-70: 42% [9%\*]; 46% [12%\*] with surgical menopause.

ie Surgery increases prevalence of distressed HSD

\* Indicates distress

# Hypoactive Sexual Desire Disorder

## Aetiology

### Biological and Psychological factors

#### Biological:

- Central (limbic system and rhinencephalon);  
Mediated by neurochemicals: dopamine (arousal) and endorphins (satisfaction);  
E2 and androgen dependent.
- Peripheral (cavernosal bodies, introitus)  
Androgen and E2 dependent. Androgens quantitatively predominate



# Hypoactive Sexual Desire Disorder

## Aetiology

### Psychological factors

- Motivational:

Recreation, reproduction, intimacy,  
'Instrumental' sex ie other benefits.

- Cognitive:

Relational factors (the nature of the relationship), beliefs, contextual factors.

# Hypoactive Sexual Desire Disorder

## Testosterone therapy

- Endogenous testosterone and sexual function may not correlate due complex aetiology
- **Androgen therapy (<24 weeks) plus E2 and Progesterone improve sexual function in postmenopausal women (particularly surgically menopausal women).**
- T therapy may protect against Ca Breast
- Adverse effects on lipids (>HDL) are associated with oral methyltestosterone

# Hormone Therapy (HT)

## Androgens for Women

### Rationale for Treatment

- Pre-menopausal women produce 300  $\mu\text{g}/\text{day}$  of testosterone
  - 50% from the ovaries
  - 50% from the adrenal gland
- Post-menopausal women produce about 150  $\mu\text{g}/\text{day}$  from the adrenal gland.

Despite treatment with E2 many postmenopausal women continue to have  $\downarrow$  libido, frequency of SI and sexual satisfaction.

# Hormone Therapy (HT)

## Androgens for Women

### Historical Perspective

- 1938 Shore noted the clinical benefit that 'libido and sexual response were definitely greater than that experienced with estradiol alone' and postulated that androgens acted on the CNS and 'at the peripheral genital level'.
- 1941 Salmon and Geist described combined E2 and T therapy resulted 'in heightened sexual desire, easier attainment of orgasm, and heightened satisfaction during intercourse'.

# Hormone Therapy (HT)

## Androgens for Women

### Historical Perspective

- 2005 The North American Menopause Society Suggested 'we may treat (androgen insufficiency) if other causes of Hypoactive Sexual Desire Disorders are ruled out'  
—
- 2006 Endocrine Society Clinical Guidelines recommended 'against making a diagnosis of androgen insufficiency and treatment of women at present' in the absence of sufficient normative, clinical and long term safety data.

Traish, Commentary, Journal of Sexual Medicine, 2007;4:1223-1235

# Female Androgen Insufficiency

## Practical Guidelines for Diagnosis of FAI

Biochemical markers:

↓ Bioavailable testosterone

E2 normal

Symptoms:

↓ well-being

lethargy

fatigue

↓ Libido

↓ Interest and blunted motivation

Princeton Consensus Statement on Female Androgen Insufficiency 2002

# Female Androgen Insufficiency

## Study

65 women (oophorectomised) with impaired sexual function, age 31-56

- T/d testosterone: 150-300  $\mu\text{g}/\text{day}$  for 24 weeks

## Results

- Low dose: increase in sexual thoughts, desires and activities.
- High dose: also improvement in mood and well-being

# Sexual Aversion Disorders (SAD)

## Definition

Severe anxiety/disgust at the thought of sexual activity

- Autonomic (neurovegetative), involuntary phobic symptoms

[cf Avoidant: voluntary with predominantly psychological factors]

- Complex causality: incest, rape, may lead to panic attacks, PTSD, asd anxiety disorders
- Older women may have SAD consequent to cultural expectations, body image, and physical health concerns about self or partner
- Stress causes secondary ↓ androgens, estrogen
- Co-morbid HSSD

Whipple, A Graziottin 2006



# Female Sexual Arousal Disorders (FSAD)

## Definition

A reduced or absent experience of sexual arousal (subjective and/or genital sensation) from any type of sexual stimulation. Hence Subjective, Genital and Combined Arousal Disorder

- Subjective arousal correlates poorly with genital congestion

Basson 2004

- **Prevalence increases with age over 50.**

**Dunn 1998**

- Aetiology: Arousal requires intact vascular and nerve supply and hormonal milieu: associated conditions include ↓ E2, DXR, urinary tract infection, pain, psychosocial factors

Whipple, A Graziottin 2006

NB Persistent sexual arousal disorder (PSAD) is a separate diagnostic category

# Promoting satisfying sex

In an older population a review of general health is particularly important in maintaining good sexual function

Hormones and chemical aids to arousal are only part of a complex social/biological system

We should consider:

- Life style factors: nutrition, exercise, 'stress'
- The relationship: communication skills, intimacy and autonomy.
- Cultural and socio-economic factors

# Predictors of sexual well-being

In women the predictors of sexual well-being relate more to relationship factors and mental health than hormonal influences

In men hormonal decline has effects on arousal centrally (brain stem) and peripherally (vascular and smooth muscle) as well as relationship factors

Sex and Aging. J Bancroft; New Eng J of Med 2007;35:820-822

OPTIMAL HEALTH  
OF  
HARLEY STREET

**Dr Michael Perring** MA MB BChir FCP (SA) DPM UKCP Registered Psychotherapist  
[www.Optimalhealth.org.uk](http://www.Optimalhealth.org.uk)  
[Mikeperring@optimalhealth.org.uk](mailto:Mikeperring@optimalhealth.org.uk)