What is the optimal therapy for young males with hypogonadotropic hypogonadism?

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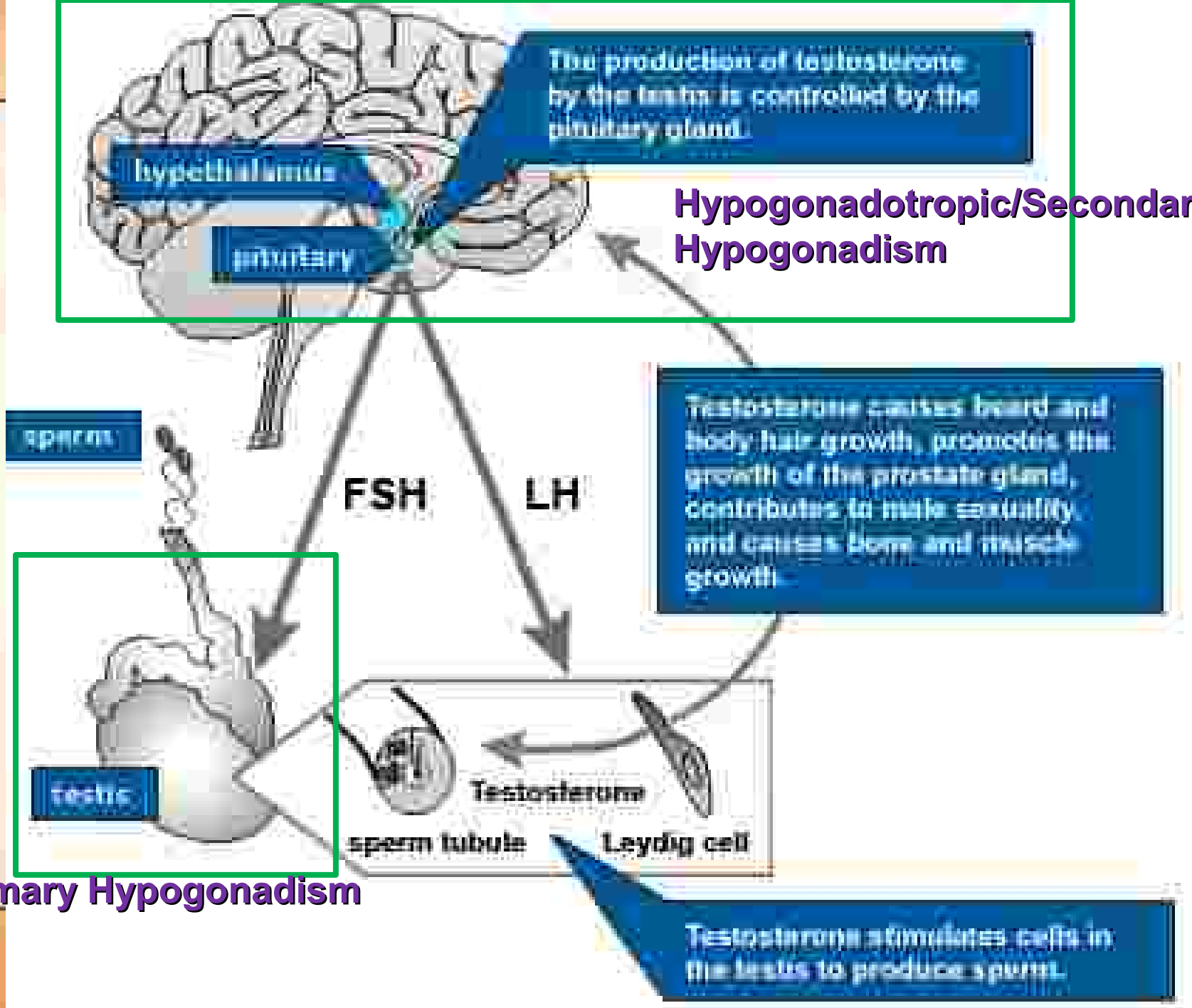

The production of testosterone by the testis is controlled by the pituitary gland.
hypothalamus
pituitary
Hypogonadotropic/Secondary Hypogonadism
sperm
FSH
LH
Testosterone causes beard and body hair growth, promotes the growth of the prostate gland, contributes to male sexuality, and causes bone and muscle growth.
testis
Testosterone
sperm tubule
Leydig cell
Testosterone stimulates cells in the testis to produce sperm.
Primary Hypogonadism

Hypogonadotropic hypogonadism

Absent or inadequate GnRH secretion

or

Failure of pituitary gonadotropin secretion

(Inappropriately low or absent LH & FSH)

Androgen deficiency *(low serum testosterone)*

and

Absent/delayed/arrested pubertal sexual maturation

Without acute/chronic illness

severe obesity &

hyperprolactinaemic states

Androgens	Activity
Testosterone	100
Androstenedione	10
Dihydroepiandrostenedione(DHEA)	5
Dihydroepiandrostenedione sulphate(DHEA-S)	5

Congenital HH

- ↓GnRH secretion (*Mono-/oligo-genic mutations*)
  - Associated with anosmia/hyposmia (Kallmann syndrome)- MRI: hypoplasia/Aplasia of olfactory bulbs
  - Isolation (idiopathic, IHH)
    - Defects identified > 10 separate genetic loci
- Part of multiple pituitary hormone deficiencies

GnRH deficiency

- Associated with full sexual differentiation at birth

Early testosterone production, GA12–20 wks, stimulated by placental hCG

- Lack two significant intrinsic GnRH surges:

1st at the late foetal/early neonatal period

- Lasting up to 6 m/o
- Leydig/Sertoli cell proliferation, Testicular growth , Scrotal descent

2nd at puberty

- Secondary sexual development, Reproductive maturity

Simple pubertal delay? True idiopathic HH?

Monogenic/oligogenic mutations

with anosmia, hyposmia or euosmia

Anosmin 1 (*KAL1*)

Fibroblast growth factor 8 (*FGF8*)

Fibroblast growth factor receptor 1 (*FGFR1*)

Prokineticin 2 (*PROK2*)

Prokineticin receptor 2 (*PROKR2*)

Nasal embryonic LHRH factor (*NELF*)

Heparan sulphate 6-O-sulphotransferase 2 (*HS6ST2*)

with euosmia

Kisspeptin (*KISS*)

G-protein coupled receptor 54 (*GPR54* or *KISS1R*)

Leptin (*LEP*)

Leptin receptor (*LEPR*)

Luteinising hormone β subunit (*LHB*)

Prohormone convertase 1 (*PC1*)

Gonadotropin releasing hormone 1 (*GNRH1*)

Gonadotropin releasing hormone receptor (*GNRHR*)

Tachikinin 3 (*TAC3*)

Tachikinin receptor 3 (*TACR3*)

Dosage-sensitive sex reversal, adrenal hypoplasia congenita, critical region on the X chromosome, gene 1 (*DAX1*)

Pituitary-specific positive transcription factor 1 (*POU1F1*)

Homeobox protein prophet of Pit-1 (*PROP1*)

Homeobox expressed in ES cells 1 (*HESX1*)

LIM/homeobox protein Lhx3 (*LHX3*)

Transcription factor SOX-3 (*SOX3*)

Defective transcription factor genes of pituitary differentiation causing combined pituitary hormone deficiency

CHARGE (coloboma, heart defect, choanal atresia, growth retardation, ear abnormalities) syndrome

Gordon Holmes spinocerebellar ataxia syndrome

Laurence–Moon–Bardet–Biedl syndrome

Möbius syndrome

Prader–Willi syndrome

Rud syndrome

Congenital hypogonadism associated with other central nervous disorders

Acquired HH

- Most frequently
  - Structural lesions of the HPA axis
  - Haemochromatosis
- Associated with multiple pituitary hormone deficiencies

Tumor

- Pituitary adenomas: MEN-I, Prolactinoma,
- Residual cell tumors: Craniopharyngiomas, Epidermoid tumours, Rathke's pouch cysts
- Gamete tumors: Germinomas, Teratomas, Dysgerminomas
- Metastases

Infiltrative

- Haemochromatosis, Sarcoidosis, Lymphocytic hypophysitis, Langerhans cell histiocytosis (histiocytosis-X)

Infection

- Tuberculosis, HIV/AIDS, syphilis, fungus

Vascular

- Ischaemia, Sheehan's syndrome, pituitary apoplexy

Trauma

- Contusion, Skull fracture, Pituitary stalk transection, Hypophysectomy

Illness

- DM, Nephrotic syndrome, Obesity, Primary hypothyroidism, Critical illness, Sickle cell disease, Thalassaemia, Alcoholism

Medical use/misuse

- Glucocorticoids, Radiation, Anabolic steroids, Narcotics

Stress

- Excessive exercise, Mental stress, Severe dieting (anorexia nervosa/bulimia), Malnourishment

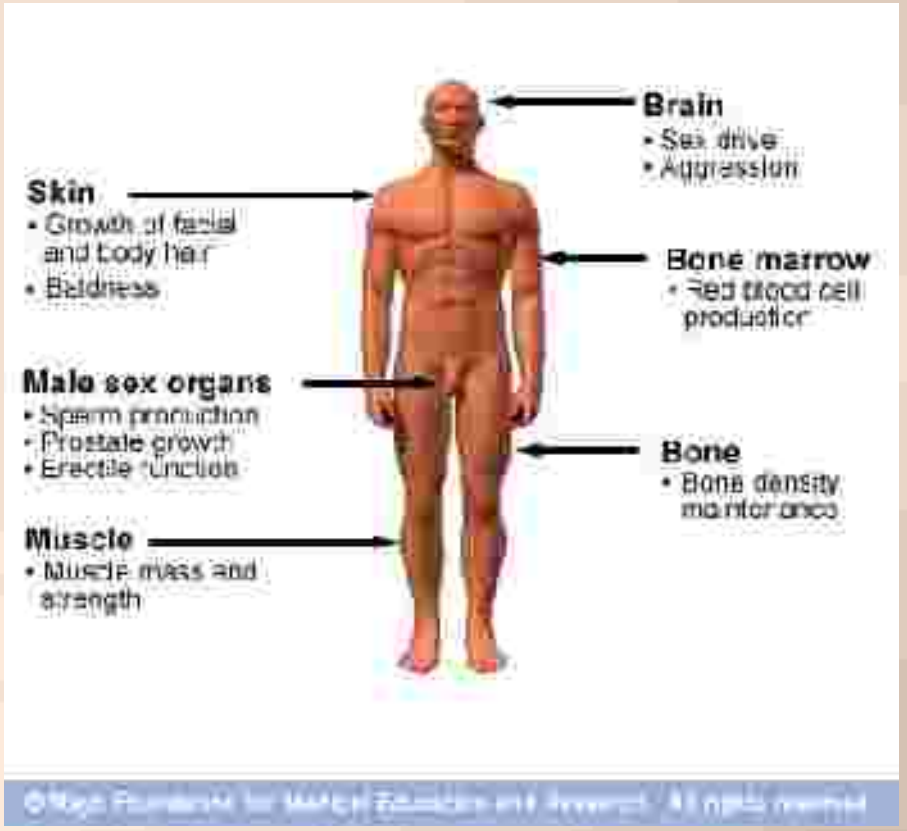
Testosterone

- 5–7 mg/day
- Pleiotropic actions
- Prohormone
  (in many tissues)

⇒ Aromatized to oestradiol
  (important for bone)

⇒ 5a-reduced to DHT
  (skin, prostate)

- Complexities of diurnal, pulsatile and cirannual rhythms



Induction of secondary sexual characteristics-TRT

- Various androgen dependent processes
  - Dose-dependency: different in different individuals
  - Normalize sexual function:
    Lower normal limit concentration
  - Fully correct low BMD, muscle mass,
    haemoglobin: Higher concentration
- Lack clinically marker of androgen action
- Improve metabolic effects(Lipids/Insulin resistance)
  ⇔Avoid unwanted effects(polycythaemia/mood swings) => Necessitate individual dose titration

- Pragmatic goal of therapy: Average serum testosterone levels restoration = 15–20 nmol/l (mid-reference range)

- Clinical markers:

(1) Restoration of sexual function (desire, frequency of erections/ morning erections, masturbation, penetrative intercourse)

(2) Secondary sexual characteristics

(3) Energy levels and sense of wellbeing

- Other consideration: Sexual counseling、fertility (lack of FSH for spermatogenesis)

Clinical challenge of managing IHH patients through the different age groups

CASE SCENARIOS

Case 1

2-month-old boy with KAL1 gene mutation

- X-linked KS in the maternal uncle
- Presents with bilateral inguinal testes

Should he have early testicular stimulation with hCG?

- Gonadotropin treatment during the first year of life

=> maturation of spermatogonia, ↑ serum testosterone

- Potential adverse effects (compromise spermatogenesis)

Treated with hCG prior to orchiopexy

- ✓ ↑ Apoptotic changes in the germ cells
- ✓ ↑ Inflammatory changes in the testes
- ✓ Smaller testes are more severely affected

- Early intervention to mimic the gonadotropic surge in the first 6 months of life: **Not indicated**

Timing and optimum management of induction of testicular descent

- Cooler scrotal environment
- Had to be early (before the age of two)

  ⇒ Maximize: Future spermatogenesis potential
  Testicular expansion

  ⇒ ↓ likelihood of future neoplasm development

- GnRH or hCG: <20% in high-lying
- Orchiopexy: 95%, risk of vascular pedicle damage

How should puberty be initiated and by what means?

- TRT: mimic the normal cadence of puberty
- Injectable i.m. testosterone: 1st line Tx of 12~13 y/o dose adjustable to match requirements at different stages of pubertal development => Avoid Mistimed epiphyseal plate closure/Persistently ↓ BMD

What is the likely impact of undescended testes on future fertility?

- Earlier orchiopexy (3m/o) > later (9m/o)
  - Testicular growth (A randomized study)
  - Subsequent quality and quantity of spermatogenesis
- Capacity for recovery is lost if the testes are left outside the scrotum too long

How should treatment be monitored and when are adult doses warranted?

- Physical assessment 3-monthly with dosage adjusted,
  ⇒ Respect the cadence of normal puberty
  ⇒ Prevent premature epiphyseal fusion(Excessive dose)
- Virilization induced/Expected adult height achieved
  ⇒ Any form of TRT can be used, (Nebido, Bayer Schering Pharma AG, Leverkusen, Germany)
- Loading 1 g i.m. q6w twice => Maintain 12g weekly

- SC implantation of 0.8–1.2 g twice a year
  ⇒ Minor surgical procedure, 10% risk: extrusion, infection, local fibrosis, scar formation
- Long-acting ester (Testosterone Enanthate or Cypionate)
  - 50–75 mg/month=>↑ *gradually every 6 months* => 100–150 mg/month=>*3–4 years* =>250 mg 3 weekly
- Oral testosterone *undecanoate* (short half-life)
  - 40 mg (with evening meal for satisfactory absorption & tendency to be 5a-reduced to DHT in the gut) → ↑ every 6 months→after 2–3 yrs→80 mg tid

- Transdermal gel
  - 1% testosterone: Testogel → 1/3 of a 50-mg satchet daily for the 1st year → ↑1/3 daily every year → final dose of 50 mg daily in the 3rd year
  - 2% testosterone: Tostran(indicated for men>18 y/o)
- Transdermal patch (2.5 mg daily, as adult doses)
  - Most closely mimic natural diurnal variation in testosterone concentrations
  - Convenient when changing from the i.m. route at late puberty to adult replacement therapy

Case 2

18-year-old male with modest pubertal development

- Euosmic, unbroken voice, eunuchoid segments
- 4 cc testes with penis stage 1
- Morning testosterone : 0.1 nmol/l
- LH: 0.1 U/l
- FSH: 0.1 U/l.

What additional investigations are warranted?

- Severe pubertal delay
- Exclude multiple defects:
  - Measure anterior pituitary hormones: PRL, TSH, IGF-1, cortisol
  - MRI
- Haemochromatosis: ferritin or transferrin saturation
- Sarcoidosis: angiotensin converting enzyme

- if HH issuspected

- Prolonged GnRH stimulation test (100 lg→500 lg i.v.)

⇒ Hypothalamic GnRH deficiency: LH/FSH gradually ↑

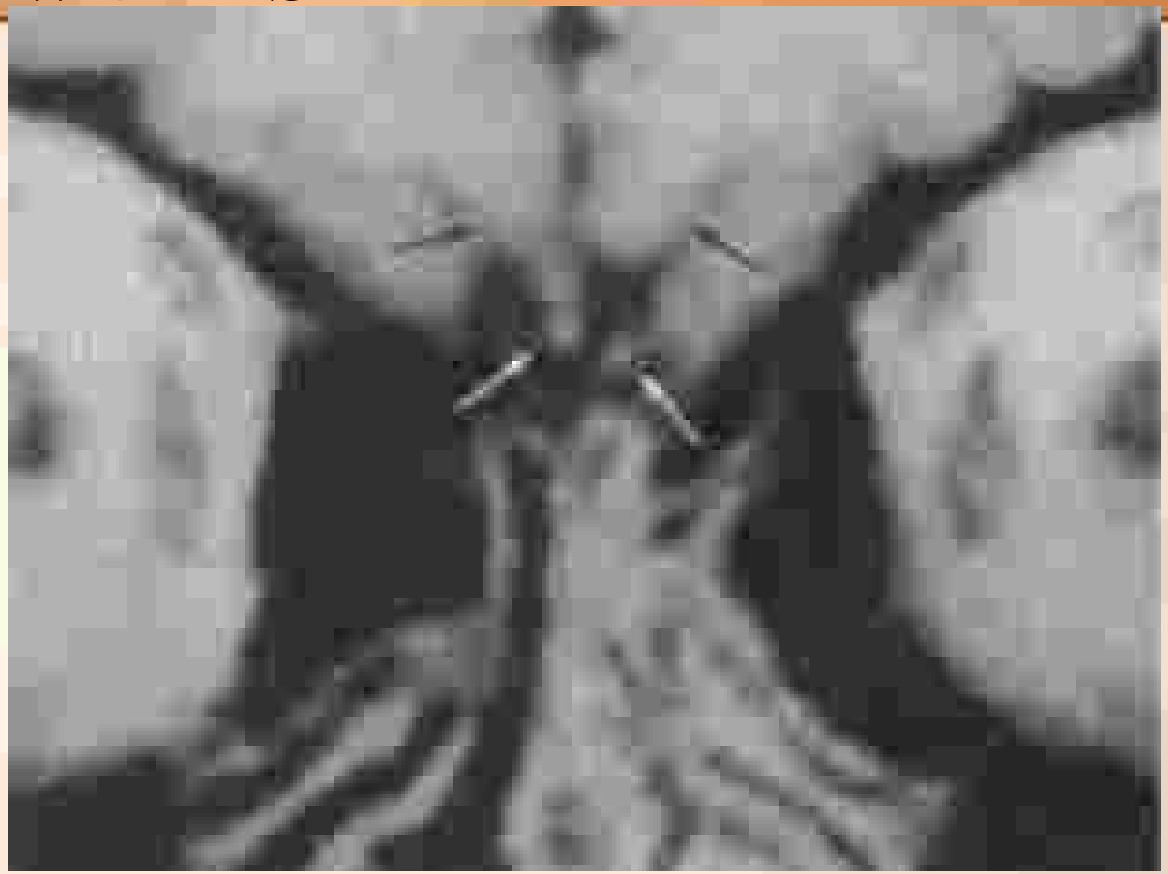
⇒ Pituitary causes *(e.g. secondary to GNRHR1 mutations or pituitary disease)*: persistent hypo-responsiveness

- Hand X-ray: Bone age
- Dual energy X-ray absorptiometry scan: BMD
- Genotyping accompanied by genetic counseling, with positive family history for known monogenic causes

Is MRI indicated in the presence of isolated HH?

- Helpful in identifying space-occupying lesions in the H-P region as well as infiltrative disorders
- Evidence of hypoplastic/aplastic olfactory bulbs and hypoplastic anterior pituitary is pathognomonic of KS (although the condition can be present even in the presence of 'normal' olfactory bulbs)
- In euosmic individuals with isolated HH:
  - Poor diagnostic yield

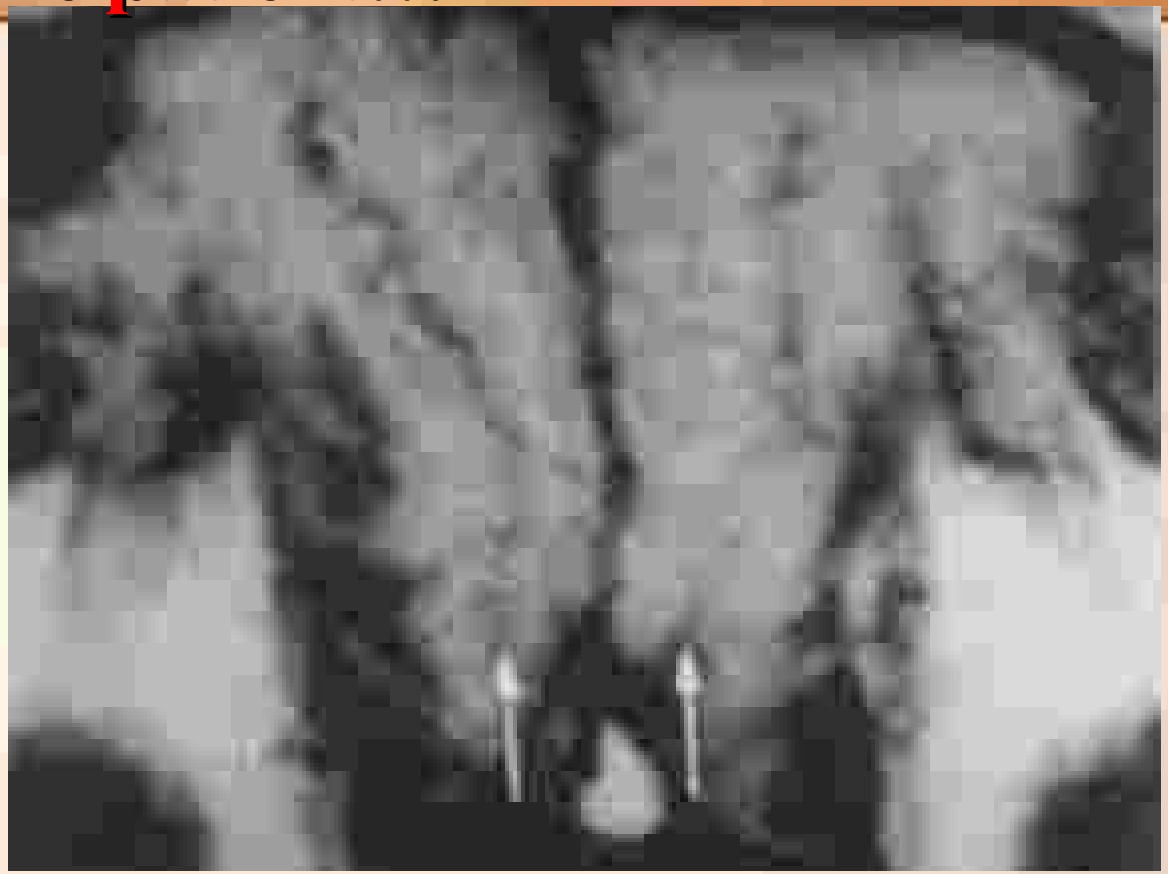
A male with KS



Coronal T1-weighted image

Abnormal angulated olfactory sulci and normal olfactory bulbs

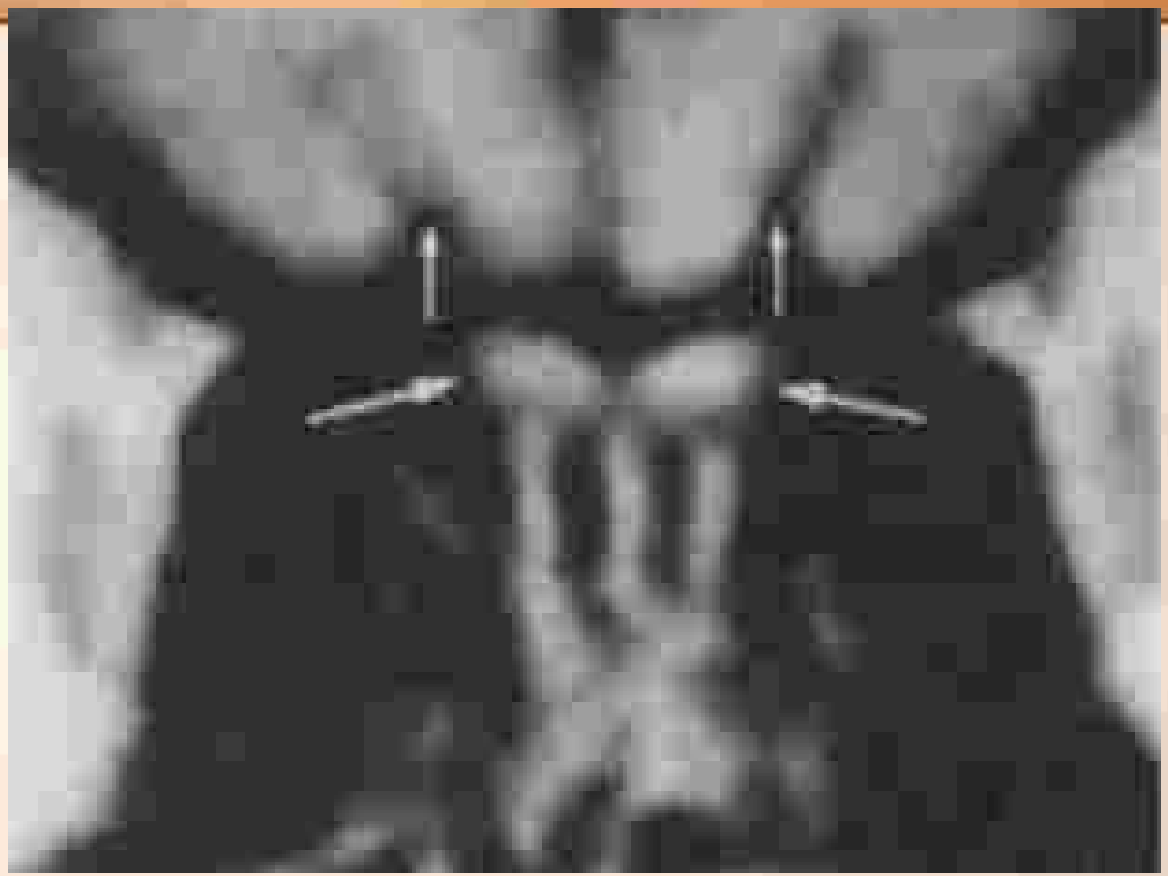
The same patient…



Axial T1-weighted image

Normal olfactory sulci

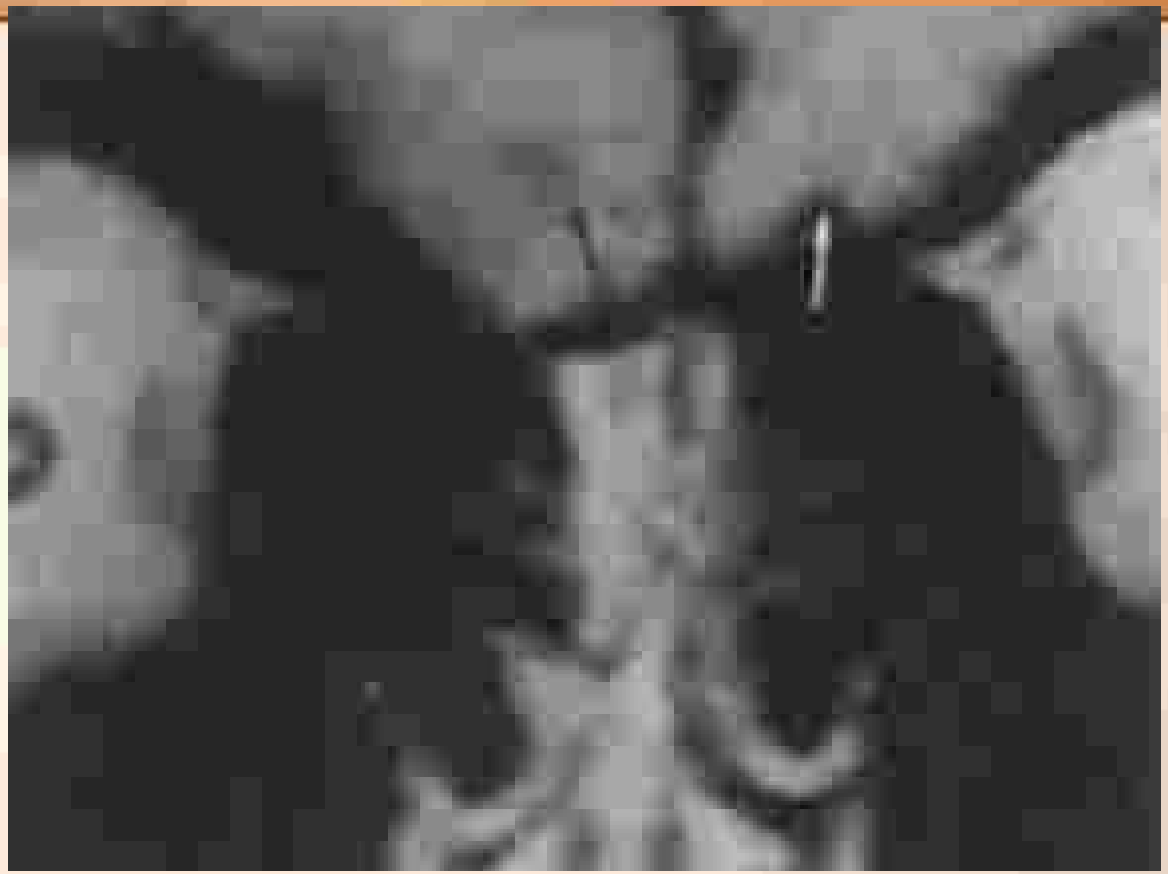
A female with IHH



Coronal T1-weighted image

Normal olfactory bulbs and sulci

A female with KS



Coronal T1-weighted image

Absent olfactory bulbs with shallow olfactory sulci

Is there an advantage to starting hCG rather than i.m./transcutaneous testosterone?

- Consider psychosocial impact of small testes
  - TRT doesn't change TV

  → hCG gradually augments TVs (suboptimal 6–8 cc)

  → Further enlargement necessitates adjunctive FSH (Expensive, usually for spermatogenesis induction)
- Ultra-longterm hCG therapy: safety profile is not established at present
- TRT may therefore be most appropriate

What is the impact of over-treatment with testosterone/ hCG on DHT and oestradiol and how is it managed?

- hCG stimulation → Testosterone over-replacement or Leydig cell androgen over-production → Excessive serum testosterone levels → elevated serum levels of DHT and oestradiol

- DHT
  - 10x potency at the androgen receptor (AR) than testosterone
  - if excess → polycythaemia, acne and seborrhoea, capital hair loss and prostate enlargement

Table 2. Monitoring of adverse effects of testosterone

Clinical ascertainment
Breast tenderness/enlargement
Acne and oiliness of skin
Symptoms of sleep apnoea
Symptoms of benign prostate hypertrophy
Mood, aggression, hypersexuality
Haematological and biochemical measurements
Haemoglobin/haematocrit
Prostate specific antigen (PSA)
Fasting lipids

- Genetic susceptibility:
  - Carriers of short CAG repeat lengths of the AR gene
  - More androgen sensitive, require lower replacement
- Polycythaemia, as evidenced by a raised Hct (>55%)
  - had to prompt ↓ testosterone dosage by about 25%.
  - Regular venesection is required when polycythaemia does not respond to dosage adjustment

Gynaecomastia

- Excessive peripheral aromatization of testosterone by adipose tissue, especially in the breast
- 1/3 of patients on gonadotropins or testosterone
- Usually during of supraphysiological replacement doses
- Risk and severity can be reversed by adjusting the dose of testosterone or hCG
- aromatase inhibitor (e.g. anastrozole 1 mg/day) or oestrogen antagonist (e.g. tamoxifen 20 mg/day) may reverse gynaecomastia if administered early
- Long-term treatment cannot be countenanced
- severe gynaecomastia resistant to Mx usually requires op

How should the prostate be monitored?

- Digital examination is essential especially if prostatic and lower urinary tract symptoms are present in the > 45-year
- TRT of hypogonadal men will ↑ prostatic volume, but provided TRT is physiological, the enlargement is no greater than that of eugonadal age-matched controls
- TRT does not appear to significantly increase PSA

- prostate cancer rarely, if ever, occurs in young men
- if urinary/prostatic symptoms occur or PSA levels rise to more than double or above 4 lg/l, a urological referral is mandated for fuller investigations
- Monitoring of other adverse effects of testosterone had to be performed routinely

Could this presentation represent very late onset puberty (i.e. extreme pubertal delay)?

- Spontaneous reversal of HH was initially observed in a proportion of non-compliant patients
- 10% of IHH: achieve sustained reversal of hypogonadism after Tx discontinuation, (although relapses can also occur)
- One possibility is that testosterone may *promote GnRH neuronal maturation*, but in many cases extreme *delayed puberty* cannot be totally excluded

- Recommend:
  - on testosterone treatment, TVs are assessed serially
  - spontaneous enlargement (gonadarche) had to prompt interruption of treatment and testosterone/gonadotropins re-measured off treatment.
  - Routine trial of **discontinuation** of hormonal therapy **for 3–6 months** to assess **reversibility** of HH may be advisable **after puberty is complete**

Case 3

32-year-old teacher with IHH & anosmia under TRT

- **TRT** Since the age of 14
- Stabilized on 250 mg i.m. testosterone 3 weekly
- Now consider fertility
- No history of cryptorchidism.
- TVs are 4 cc bilaterally

How should spermatogenesis be induced and what doses of gonadotropins are needed?

- hCG: stimulate testosterone synthesis, widen the seminiferous tubules, ↑ primary spermatocytes
  - 1500 IU s.c. twice weekly (some require up to 10,000 IU for normal testosterone levels)
  - Alone → semen production (larger pre-treatment testes, >8 cc, no Hx of cryptorchidism)

probably reflecting incomplete FSH deficiency

If severe oligospermia or aspermia persists after 3–4 months

- FSH, 150–225 IU, s.c. or i.m. thrice weekly for 6–24 months (or r-FSH, s.c., 150 IU thrice a week)
- Combination of hCG/FSH therapy, 6–24 months → testicular growth in almost all, spermatogenesis in 80–95% (pt without undescended testes)
- Equally effective when given s.c. (↑ pt's compliance)

- GH:
  - May have a direct effect on Leydig cells
  - r-human GH may augment Leydig cell response to hCG
  - Little evidence in improved spermatogenesis outcome

What sperm concentration is likely to result in pregnancy and what are his fertility prospects?

- Factors predicting successful outcomes
  - Larger baseline testicular size, Absence of cryptorchidism, Prior Hx of sexual maturation, No prior androgen therapy

- Patients with smaller than normal TVs(even < 3cc)
  → achieve sperm counts below the reference range
  → 0.5–1.5 million/ml can be fertile
  → 5 million/ml, pregnancy rates 50~80%

- Assisted reproductive technologies in poor responders
- Commence induction 6–12 months prior to a planned conception (natural/IVF/ICSI)
- Sperm storage in good responders who are contemplating adding to their family
- Genetic counselling may be needed prior to spermatogenesis induction

Is there an advantage to using pulsatile GnRH therapy?

Pulsatile

- s.c. into the abd. wall q2h, 5 lg/pulse, ↑2 lg every 4 weeks until physiology [LH] & [FSH]
- Monitor [testosterone] in 6–8 weeks, will ↑ significantly within 3–6 months, sperm appear in the ejaculate 18~139 wks

GnRH vs gonadotropins

- May stimulate testicular growth at a faster rate
- No advantage on achieving final TV, onset of spermatogenesis, sperm counts or pregnancy rates

- hCG/FSH or pulsatile GnRH regimen
  - patient's preference and pharmaco-economic factors
- GnRH therapy:
  - Unlicensed, available only in few specialized tertiary centres. More expensive. Inconvenience of pump use, rotate infusion site, interference with patient lifestyle

When should stimulation treatment be stopped?

- Until at least the 2nd trimester
- Spermatogenesis induced by the combination of hCG and FSH or GnRH can occasionally be maintained with hCG alone
- If long delay before pregnancy =>long-acting i.m. testosterone ester, with advice on contraception => Sperm storage (for IUI or ICSI)
  =>Spermatogenesis can be re-initiated with hCG in some cases

Should antenatal diagnosis of the unborn child be considered?

- Genetic counselling

⇒ If the individual belongs to a pedigree with HH or where HH occurs with a recognizable syndrome

⇒ Genetic testing

Case 4

28-year-old man with haemochromatosis

- Referred due to sexual malfunction
- Little secondary sexual hair
- 5 cc testes with a normal phallus
- Ferritin: 2600 lg/l
- LH: 0.4 U/l, FSH: 0.3 U/l, testosterone: 1.2 nmol/l, SHBG: 98 nmol/l

Iron deposition → Damage to the H-P axis
(before being deposited in the pituitary and testes)

How should his hypogonadism be treated?

- Restoration of sexual function and fertility

⇒ Sexual function: 50 mg of daily Testogel or Testimwould
(Physiological concentrations: 0.5–2 sachets/day)

⇒ Fertility: Gonadotropins

- ➢ FSH secretion intact at an early stage → hCG to Initiate Spermatogenesis
- ➢ Significant iron damage → Testosterone production/spermatogenesis may be suboptimal

- General well-being and psychosocial aspects

What are his prospects for reversal of hypogonadism with venesection?

- Prevents further damage to the pituitary and testes from iron deposition
- Repeated venesection to normalize ferritin levels can **reverse** hypogonadism in some patients with iron deposition particularly in those below 40 years old

CONCLUSIONS

Optimal management of young HH males

- Elucidation of the underlying aetiology
  - Mutations within key candidate genes in the H-P axis
  - Structural abnormalities in the H-P region (usually with multiple pituitary hormone deficiencies)
- Regular monitoring
  - Impact of the condition on long-term health
  - Psychosocial function

Choice of therapeutic intervention

- Based on the individual's requirement
- Puberty:
  - ⇒ Induced by low i.m. doses of testosterone initially
  - ⇒ Followed by upward titration
- Fertility:
  - ⇒ Induced by HCG, FSH preparations, Pulsatile GnRH

Testosterone replacement therapy

- Likely to be life-long
- Requiring regular monitoring for
  - Optimization
  - Avoidance of adverse responses
- Patients with reversible phenotype (a small subset)
  ⇒ May enable withdrawal of therapy ~ 10% of cases

THANK YOU FOR TOUR ATTENTION

THE END