Puberty and CHARGE Syndrome

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Presenter Information

Prof. Jeremy Kirk is a Consultant Pediatric Endocrinologist at Birmingham Women's and Children's Hospital, with a special interest in growth and pubertal disorders. He has published chapters in the US and German CHARGE books as well as online resources in the UK. Jeremy has been the Medical Advisor to the UK CHARGE Syndrome Family Group and has organized a number of national conferences. Jeremy also established the first UK national pediatric and also adult multidisciplinary CHARGE clinics in Birmingham, plus national screening for CHD7.

Presentation Abstract

Pubertal issues are common in CHARGE syndrome, and especially in males. Characteristically sex hormone replacement (when required) is the standard treatment, although this is non-physiological, often started late, and may not produce optimal results. Recently, therapies which more closely mimic normal hormone production are being developed and utilized.

Data will be shown on variation in current treatment between different units and countries. Although there is little data on outcomes in CHARGE syndrome, overlap with other similar conditions such Kallmann syndrome gives insight in to how these therapies might work.

Learning Objectives

- Understanding the underlying puberty hormonal issues in CHARGE.
- Looking at current and potentially new therapies which might optimise outcomes.

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Puberty and CHARGE

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The talk

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1. Background:
    1. *Hormones*
    2. *Puberty..*
2. Hormone replacement therapy (HRT)
3. UK experience
4. Controversies and planned research

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Hormones and Puberty

What is a Hormone:
Wikipedia

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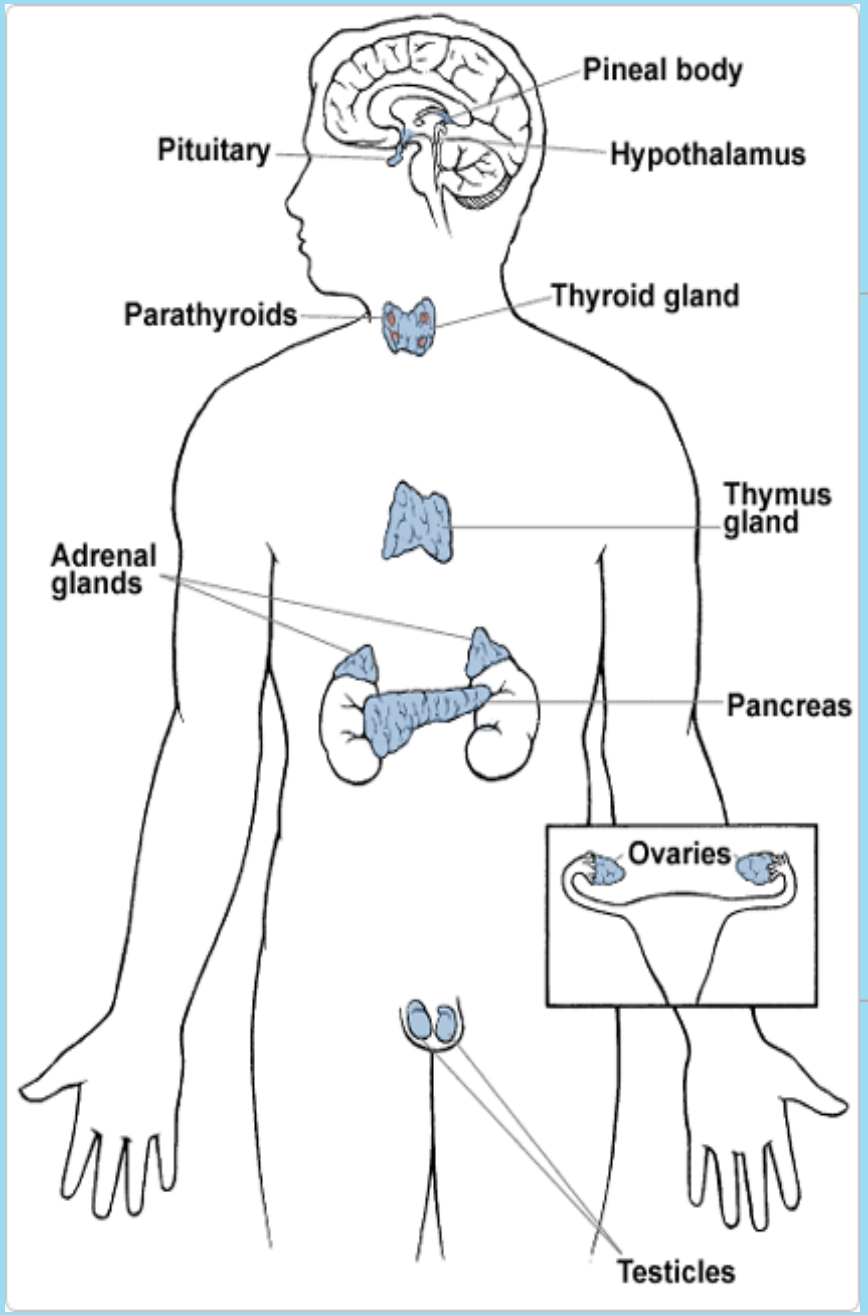
- "A **hormone** (from the Greek *ὁρμή* - "impetus") is a chemical released by a cell or a gland in one part of the body that sends out messages that affect cells in other parts of the organism".
- Endocrine hormones are secreted (released) directly into the bloodstream.



Endocrine system glands

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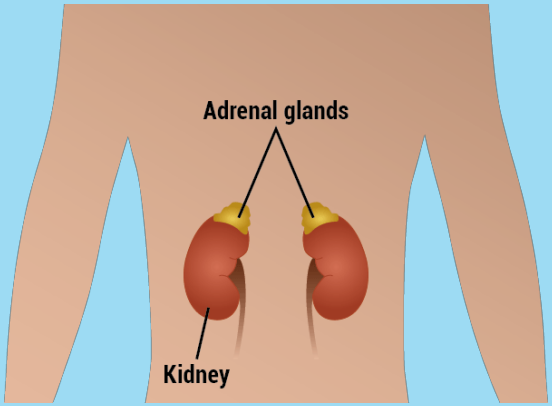
Sex hormones are produced from 2 endocrine glands:

1. **<u>Adrenal glands</u>**

Produce androgens:

1. Pubic and axillary (armpit) hair
2. Acne, greasy hair and skin
3. Adult body odour
4. Mood swings.



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2. Gonads (ovaries in girls, testicles in boys)

- Growth spurt in both sexes (mediated via oestrogen)
- Breast development in girls (mainly oestrogen)
- Genital development in boys.

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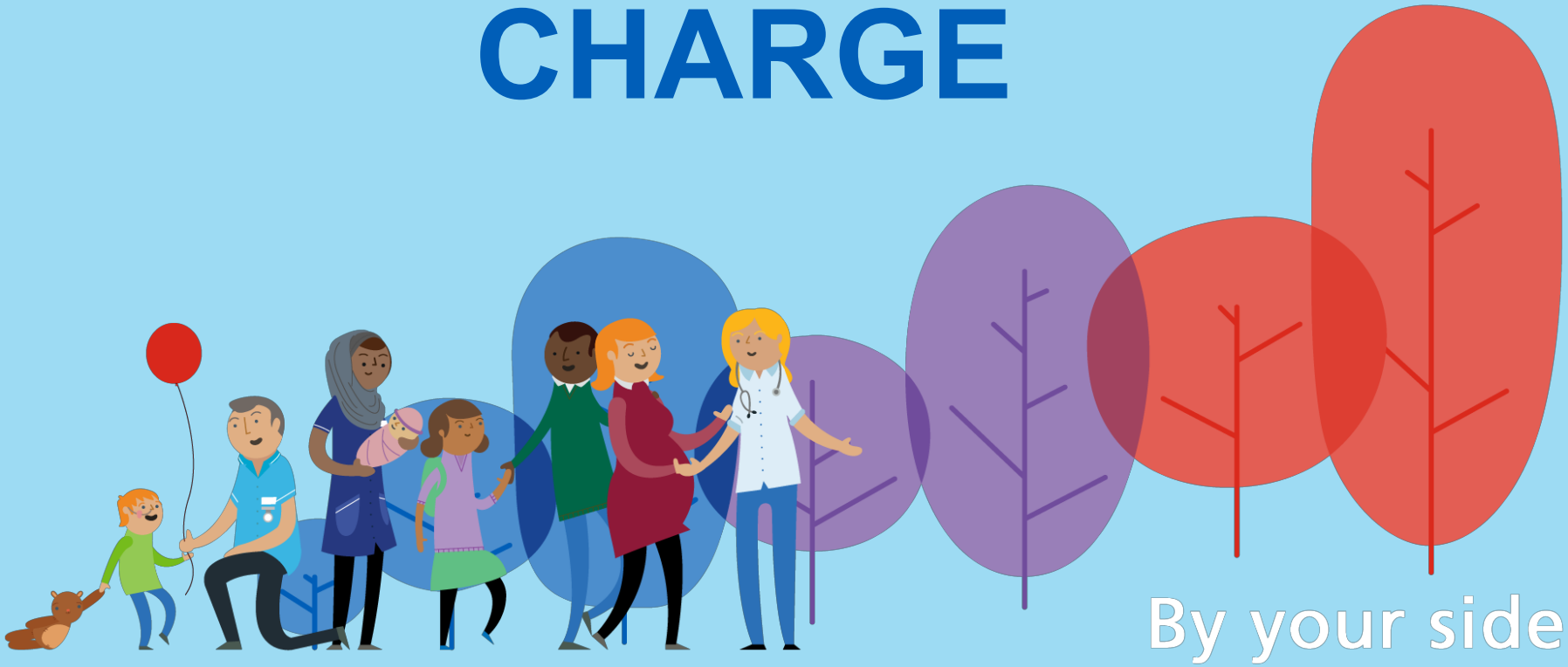
Puberty and CHARGE



By your side

Pointers to puberty problems

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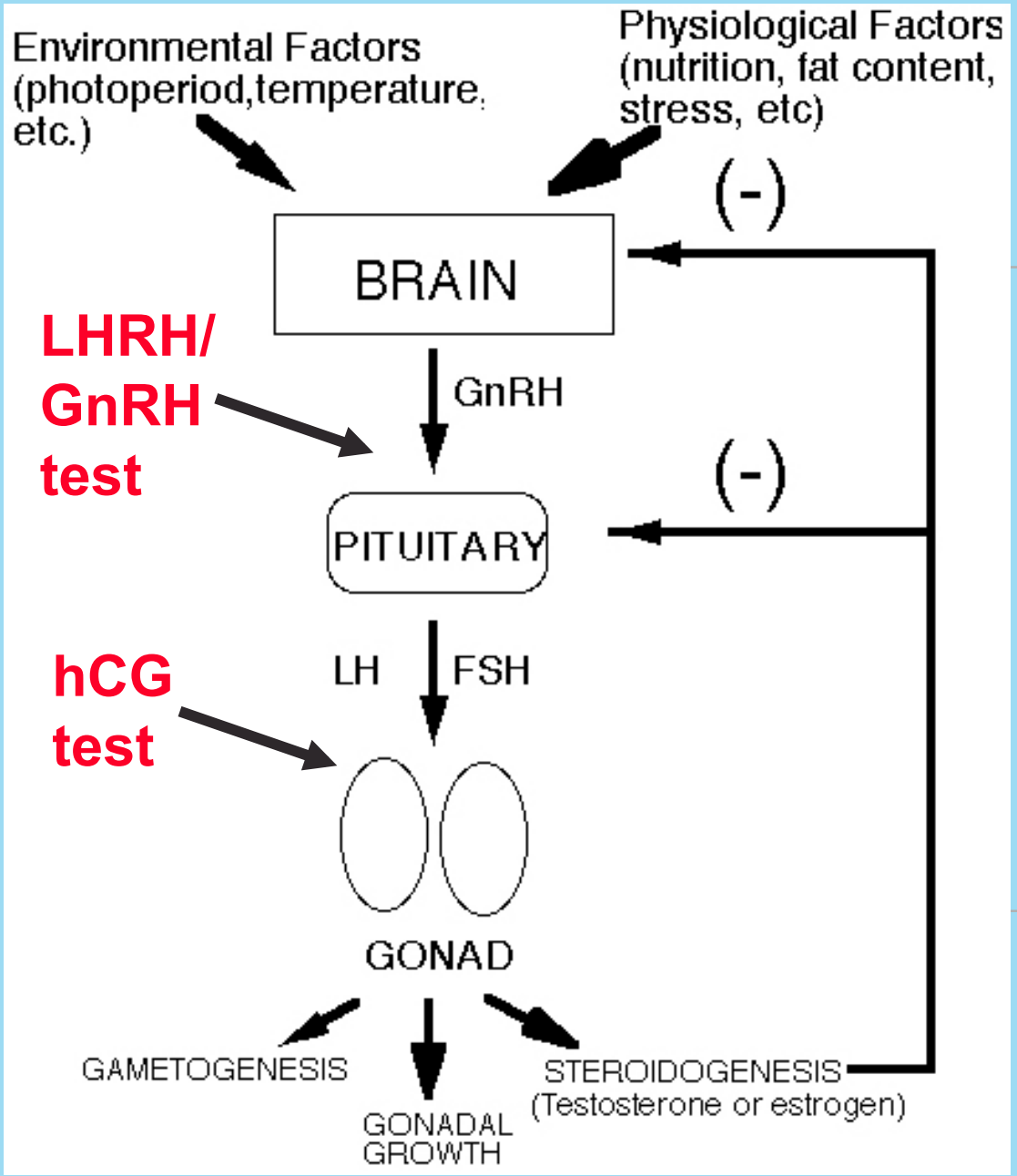
- Anosmia (absent sense of smell) in both sexes.
- Micropenis (pinch an inch?) }
- Undescended testicles } in males.

- NB: Remember that pubic hair alone "adrenarche" may be due to sex hormones arising from the adrenal glands.



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Hormones involved in genital & puberty development & fertility

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Hormone Replacement Therapy (HRT)

Puberty

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Remember:

- Testosterone itself won't produce enlargement of the testicles.
- Gonads also are responsible for reproduction: eggs (ova) in girls, sperm in boys.
  - Girls are born with a full complement of eggs
  - Boys testicles produce sperm after puberty

HRT: Concerns in CHARGE

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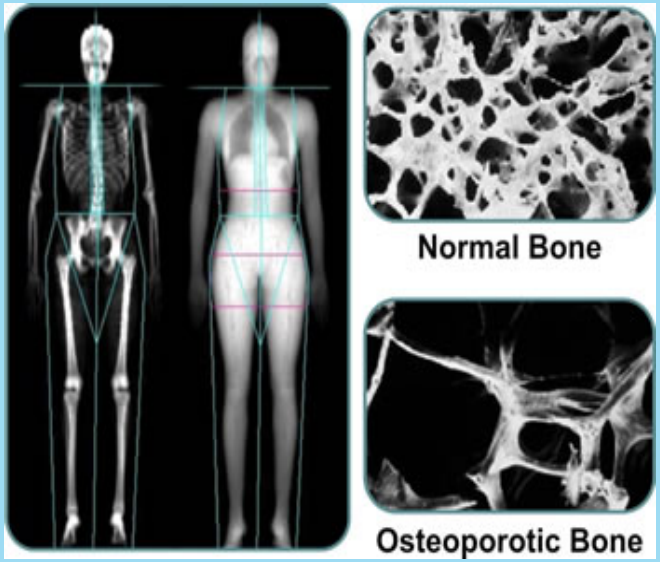
- Worsening behaviour.
- Inappropriate sexual behaviour.
- Menstrual bleeding (in girls).
- Persistent erections (priapism) in boys.

Must be balanced against long-term osteoporosis risks as much bone strength is laid down in late teens under the influence of sex hormones.



Hormone replacement in girls

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Controversies

- Natural or synthetic estrogen?
- Oral or patch?
- Hormone replacement therapy (HRT) or oral contraceptive pill (OCP)?

HRT in boys: Options

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- Injection:
  - Monthly
  - 3 monthly
- Oral
- Patch
- Gel

Testosterone levels after standard testosterone injection

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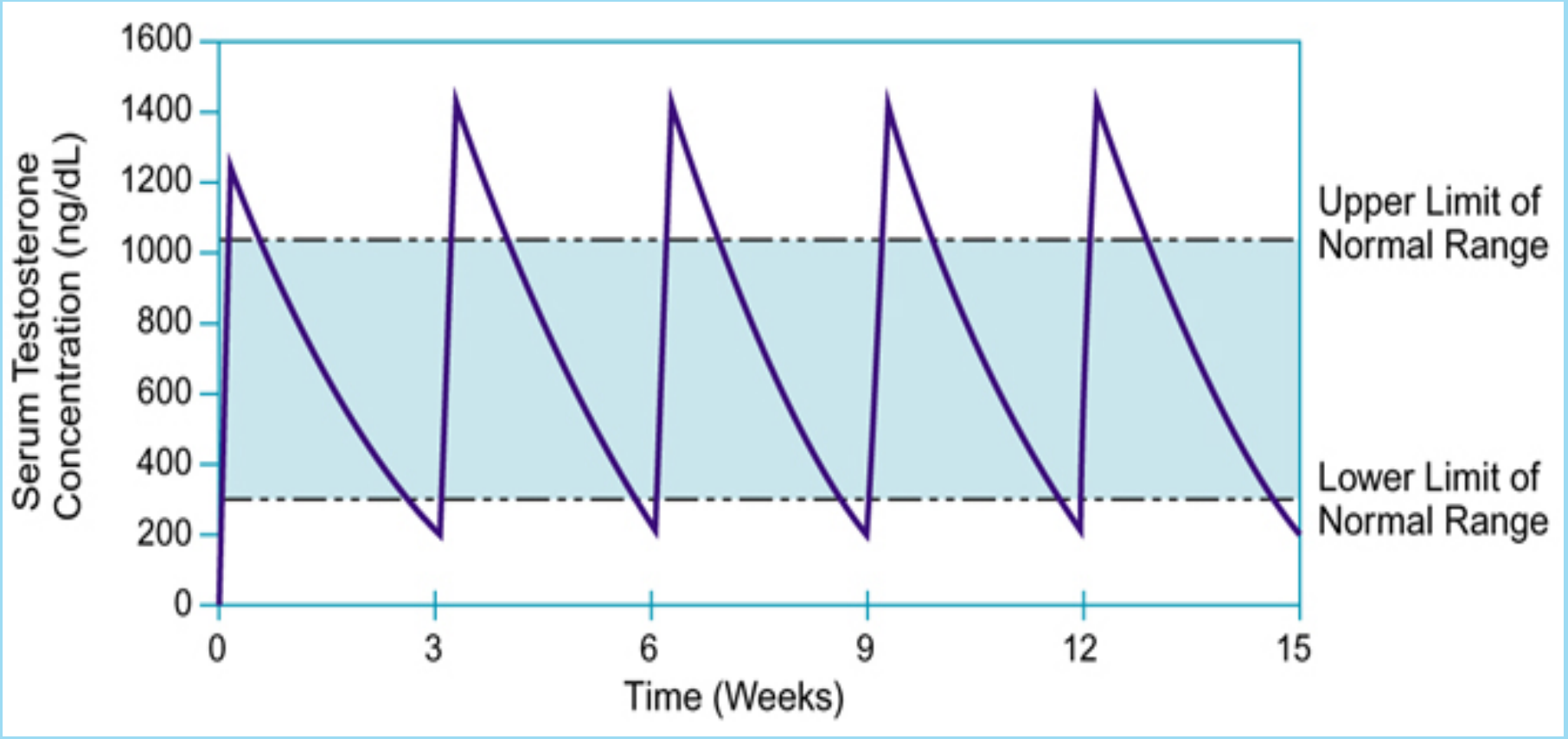

Testosterone levels after long-acting testosterone

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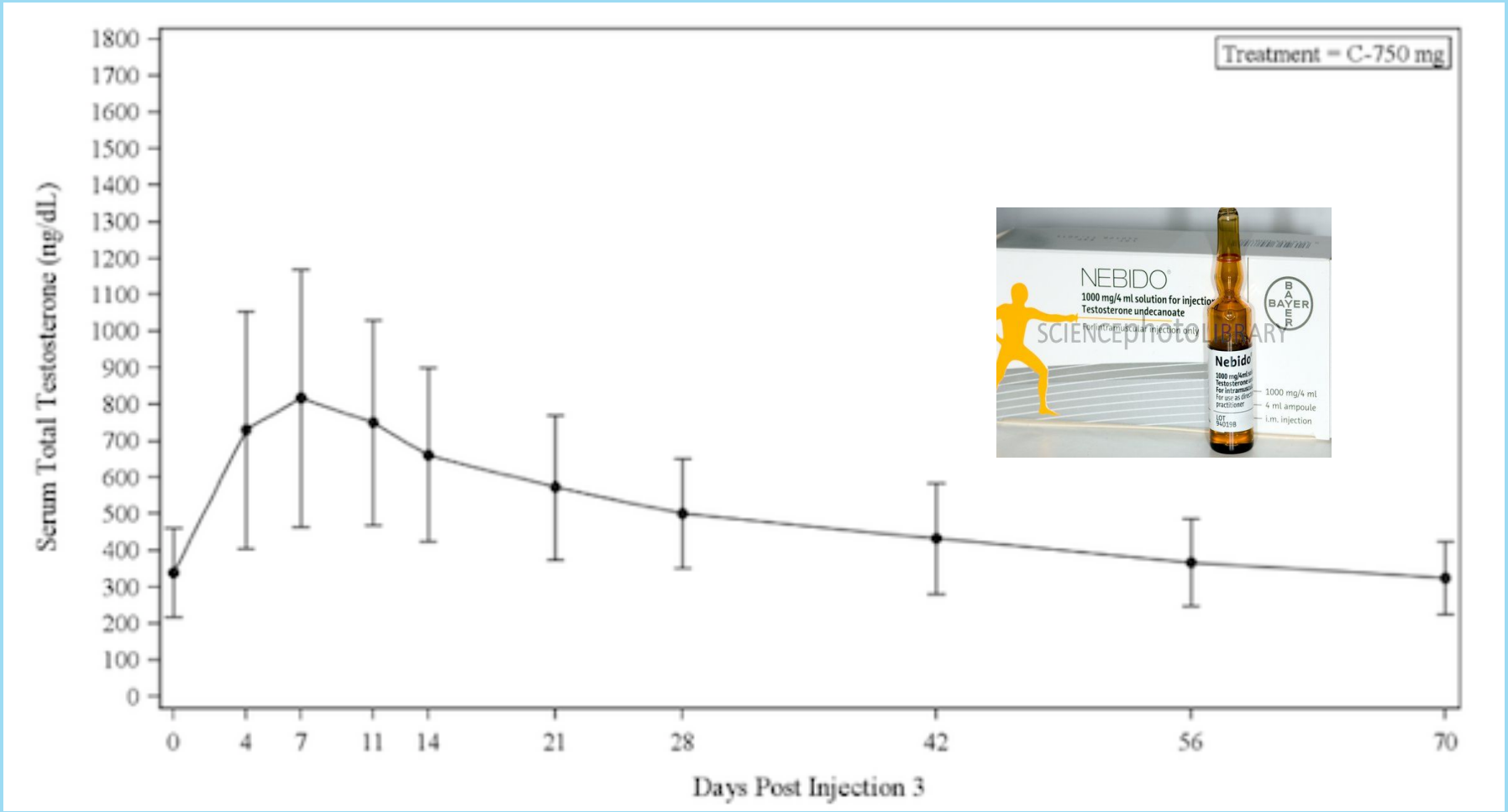
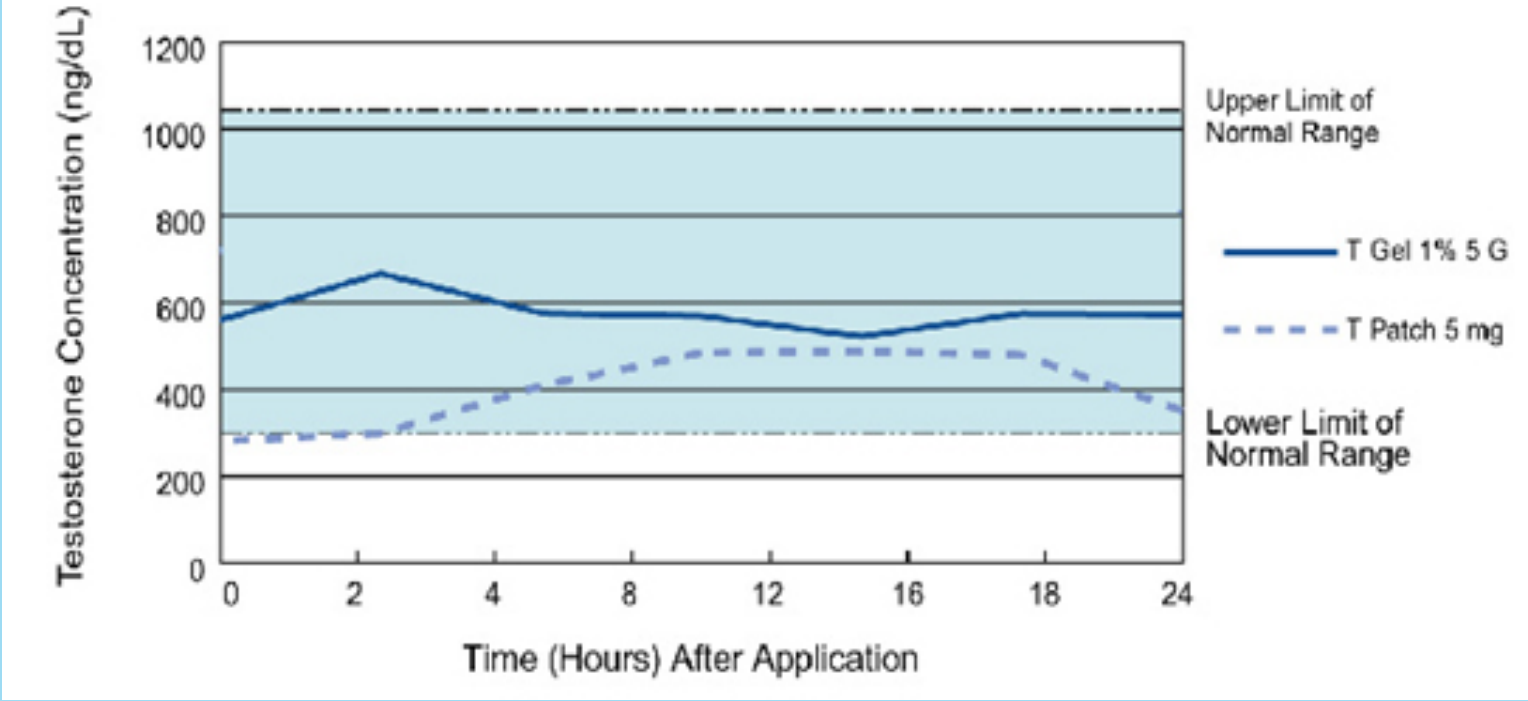


Testosterone levels with patch and gel



When to start

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- Normal puberty starts at around 10-11 years in both boys and girls, and lasts for around 3 years.
- Delayed puberty is defined as lack of puberty:
  - By 13 years in a girl (or 15 years to start periods).
  - By 14 years in a boy.

When to start

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- Probably inducing puberty over a number of years is preferable to doing this over a shorter period of time.
- If a child is likely to have delayed or absent puberty (as in CHARGE) is it appropriate to wait until they have fallen out of the normal range before treating?
- Probably best to bring on puberty slowly over a number of years, starting from 10 to 12 years of age, than waiting until 13-14 years of age.

UK Experience

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- Details on 60 children (21 females).
- Average age of referral was 4.3 years (range birth to 17 years), with main reasons for endocrine referral being:
  - Short stature in 66% (N=40)
  - Micropenis/undescended testicles in 76% of boys (N=26)
  - Delayed puberty in 40% (N=24)
  - 3 were under routine endocrine follow-up.

UK Experience

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- 80% of the boys with micropenis and/or undescended testicles required assistance with puberty.
- The only boy that underwent puberty spontaneously did not have micropenis and only had one undescended testicle.

UK Experience

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- Details on 30 children (17 boys) of pubertal age.
- 20% achieved spontaneous puberty; only 1 was male.
- Boys much more likely than girls to require assistance with puberty (93% vs. 64%) (P=0.05).

LHRH testing in CHARGE (N=14)

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UK Experience

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- Median age at pubertal induction was 13 years (Range 12-17.5).
- 10 children were induced at or beyond 14 years of age due to delayed presentation.

UK Experience

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BOYS

- 8 received intramuscular (im.) testosterone.
- 5 received oral testosterone.
- 2 received topical testosterone gel.

- In 2 boys therapy was changed from im. to topical due to worsening behaviour.

What's the best way to induce puberty in boys?

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- As the defect is central (gonadotropin deficiency) the logical physiological treatment would be gonadotropin therapy;
- this however requires regular (several times weekly) subcutaneous hCG injection,
- whereas testosterone therapy requires (at most) monthly injection.

hCG vs. Testosterone

- United Kingdom generally treats with testosterone
- Netherlands treats with hCG
- So which is the best?

Neonatal gonadotropin therapy

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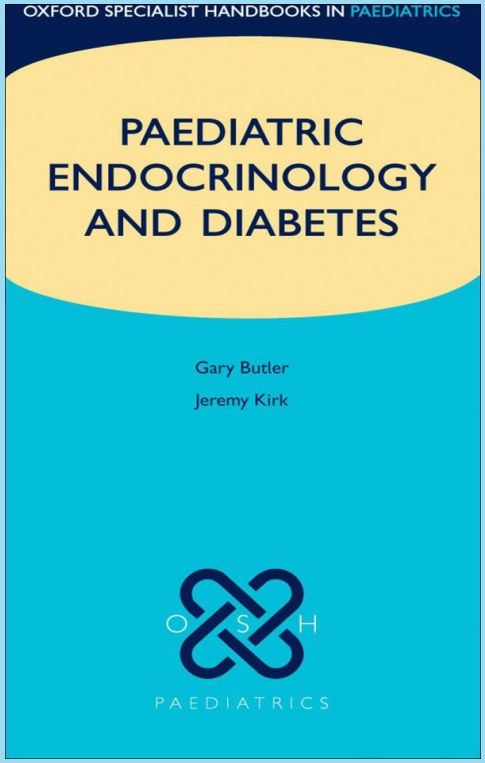
The same hormones are involved in:

1. descent of the testicles and growth of the penis prior to birth in boys.
2. a ‘mini-puberty’ in the first 6 months of life.

Should we therefore be giving gonadotropin therapy after birth to boys with hypogonadotropic hypogonadism?



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Thank you!

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