Congenital Hypogonadotropic Hypogonadism (CHH): the Adult Perspective

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I attended ICE Capetown as a guest of Bayer UK
My role today is to outline to you what happens to CHH men and women beyond the Introduction and Chapter I.
Summary of this Presentation

1. How do men and women with CHH really feel?

2. And why might they feel that way?

3. Differentiating CHH from Constitutional delay.

4. Treatment of pubertal delay in the 17+ age group

5. Role of Imaging and Genetics

6. Fertility prospects and obstacles
My Pet Hates in DSD & pubertal delay

1. GnRH tests
2. hCG tests
3. Bone age
4. Pelvic imaging & karyotype - unless raised FSH
5. Ethinylestradiol for pubertal-induction
6. COCP for maintenance HRT
Age-related presentation of male hypogonadism

FETUS

- GnRH/LH/T secretion

INFANT

46XY DSD: externally ♀
- hypospadias, etc
- hCG-driven T secretion / action from 7 weeks
- fetal GnRH from 8wks pre- to 6m post-partum = “minipuberty”.

CHILD

- absent 2° sex characteristics
- eunuchoidal proportions
- gynaecomastia
- small testes

PUBERTY

- GnRH axis re-awakens

ADULT

- libido
- bone mass
- muscle mass
- energy level
- anaemia
- infertility
Idiopathic / Isolated / **Congenital**
- Hypogonadotropic Hypogonadism
- GnRH / Gonadotropin Deficiency

**IHH / CHH / IGD / CGD definition:**
- h/o failure to properly initiate puberty
- low serum Tor $E_2$ with low or “normal” LH+FSH.
- otherwise normal pituitary structure and function.
- all other $2^0$ causes excluded.

**Aetiology:**
- Congenital / Genetic defect of GnRH secretion or action.
  - 30+ genes, underpinning ~50% of cases.
  - high prevalence of cryptorchidism due to absent minipuberty.

**Non-reproductive phenotypes:**
- found in 60%, most commonly anosmia = Kallmann’s (KS)
CHH: age at meaningful diagnosis

18-19 year median also seen in a web-based survey by Dwyer, Clin Endo 2017
Neil's Story

- Age 1 year underwent orchidopexy.
- Age 15–17 years: consulted GP x4, lacking puberty.
  - Repeatedly reassured or concerns dismissed.
  - Eventually referred to Paeds age 17.5 years.
  - Received 6 x 50mg IM monthly.
  - Some virilisation & testes now 4mL, so onset of endogenous puberty assumed & discharged from F/U.
- Drifted thru Uni, socially isolated; under-achieved academically.
- Presented age 25: arrested early puberty and CHH.
- Started T replacement, but took 15+ years to navigate grief response and gain confidence for physical relationships.

Follow Russell on Twitter @RCPCHPresident

Boys aged 15 or over with a testes >4 mL can be reassured that puberty is beginning. Those with no signs of puberty by age 15 should be referred for further investigation.

Viner, ABC of Adolescence, 2005
Amy’s Story – part I

10 amenorrhoea at age 13.5 years & seen by Paediatrician:
- signs of early puberty (B2 P2 A1), but otherwise healthy.
- linear growth preserved, but no growth spurt.
- LH, FSH & E₂ all <1.0, but otherwise normal pituitary, etc.
- Amy doesn’t have a sense of smell.

Paediatric Consultant opinion:
- as puberty has begun, constitutional delay is most likely. ¹,²
- for bone age, karyotype, pituitary MRI, pelvic USS. ¹,²
- no treatment required unless still no progress after age 14. ¹,²
- If treatment is required, we’ll give Ethinyloestradiol (EE₂). ³

¹. BSPED+SfE guidance on DSD – Clin Endocrinol, 2016
². ABC of Adolescence – Viner R, BMJ, 2005
³. Pubertal Induction in Girls – BSPED 2016
Amy & Mum disagree - do you?

- Congenital anosmia + 10 amenorrhoea + low LH & FSH (CHH) = Kallmann syndrome until proven otherwise.
- Contrary to ABC: “started puberty” doesn’t always complete.
- 1/3 of CHH patients have partial puberty (testes >4 mL, or B2-3),
- **Amy is on the wrong clinical pathway:**
  - Delayed Puberty ?cause – *Watch / Investigate* instead of:
    - Presumed Hypogonadism – *Induce Puberty!*
  - Low-dose E2 should ideally have been initiated by age 12.
  - No useful contribution of karyotype and bone age.
  - Pelvic USS just causes anxiety if immature uterus not seen.
  - Pituitary MRI =OK, but do coronal T2 through olfactory bulbs.
T2-weighted coronal MRI

Sinusitis

Kallmann’s
Health Perceptions & QoL in CHH

Lots of anger directed at past doctors who dismissed them as late bloomers, or gave false reassurance.

Intense regret that they or their parents hadn’t been more assertive in demanding / achieving treatment.

Psychosexual issues are common:

- Body Image concerns/shame $\rightarrow$ 87%
- difficulty with Intimate Relationships $\rightarrow$ 66%
- moderate-severe Depressive symptoms $\rightarrow$ 30%

Men with CHH report even worse outcomes:

- Psychological distress comparable to end-stage CCF or COPD.
- Never in a relationship? 23% vs 7% of women $^*$  $^*$ p<0.05
- Never been sexually active? 26% vs 6% of women $^*$

*Dzemaili, Endocrine Connect, 2017*  *Dwyer, Sex Med, 2015*  *Varimo, Clin Endo, 2014*
Distinguishing CHH from CDP and DP?

Look for the red flags present in 60-70% of CHH cases:

- **Historic indicators of absent minipuberty:**
  - Microphallus (10% - 0.15% UK birth prevalence)
  - Cryptorchidism (40% - 4% at birth; 1.5% at 3 months)
  - Bilateral cryptorchidism (20% - 2% at birth; 0.4% by 3-12 months)
  - Absent erections on morning nappy change

- **Non-reproductive phenotypes associated with CHH**
  - Anosmia (45% - 2% UK prevalence, but not exclusively congenital)
  - Deafness (6% - 0.12% UK births - otoacoustic emission test)
  - Cleft lip or palate (5% - 0.15% UK birth prevalence)
  - Syndactyly, clinodactyly, etc. (5% - 0.1% UK birth prevalence)
  - Family history of CHH, e.g., child born from sperm induction Rx.

**Composite data:**

~5% of boys with bilateral cryptorchidism at 3 months will turn out to have CHH

Swee & Quinton, Therap Adv Endocrinol Metab, in press

In CPHD male infants, low LH, FSH & T identified CHH with 93% sensitivity & 100 specificity

Bravlasky, Horm Res Paediatr, 2015

FSH+hCG infusion induced testicular descent in 7/8 CHH infants with cryptorchidism

Lambert & Bougnieres, Intl J Ped Endocrinol, 2016
Pubertal Delay in the over 19s

CDP isn’t part of the Differential diagnosis:

• >90% have congenital hypogonadism:
  – in males, 99% of hypogonadism is hypogonadotropin or 20.
  – both 10 & 20 hypogonadism seen in females

Normal tempo of puberty over 2-3 years does not apply.

• Aim to complete puberty within 1 year in males
• Concerns about behaviour change = MYTHICAL.
• Adopt protocols from Gender colleagues, not Paedriatrcs.
Ethinyl Estradiol?

- Has been used to induce puberty **only in UK**
- Levels cannot be measured in serum.
- Less successful than $E_2$ at achieving uterine maturation.
- Powerful GH-antagonist.
- Activates Renin, so risk of hypertension.
- Pro-thrombotic, so risk of VTE.
- Analogous to inducing puberty in boys with **nandrolone**.
- Very expensive
- **What’s not to like about it?**
CHH Genes 1991-2015

1998

2002

2008

2015
Neuroectoderm
Olfactory axons
Neural crest
GnRH neuron precursor

Olfactory bulb
Cribriform plate
Olfactory tract

Median eminence
Pituitary gland

Adapted from Stamou et al, Endo Rev 2015 Sep 22:er20151045
Neuroectoderm

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Neurodevelopmental:
- SEMA3A, FEZF1, CHD7
- FLRT3, IL17RD, KAL1, SOX10

Neuroendocrine:
- KISS1/KISS1R, DAX1, TAC3/TACR3, GNRH1

Both:
- FGF8/FGFR1, PROK2/PROKR2, WDR11, AXL, NSMF, DUSP6, SPRY4, FGF17

Kallmann
- KAL1 neuron
- Cribriform plate
- Olfactory bulb
- Olfactory tract
- Neural crest
- CHD7, SOX10

Hypothalamic GnRH neurons
- Median eminence
- Gonadotrope stimulation
  - DAX1, GNRHR

Pituitary gland

Adapted from Stamou et al, Endo Rev 2015 Sep 22:er20151045
Human spermatogenesis requires both FSH and \textit{umolar} locally-secreted paracrine T. It can’t be sustained by \textit{nmolar} circulating endocrine T.

\textit{Schaison, Young, et al, JCEM, 1993}
Sexual Dimorphism in Gametogenesis

Females *in utero* have already achieved their lifetime supply of “ready to go” oocytes,

BUT

To develop & sustain normal spermatogenesis, males need to have undergone 3 distinct phases of testicular maturation
Triphasic Maturation of Testes

1. From Gest. 7 weeks = external male sexual differentiation:
   - placental hCG drives Leydig cells to secrete T.
   - GnRH neurons migrate from nasal placode to hypothalamus.

2. Gest. 32 weeks – 6 months post-natal = Minipuberty:
   - fetal–neonatal GnRH secretion ⇒ pituitary FSH & LH.
   - serum LH, FSH & T levels are adult mid-puberty range.
     ⇒ germ & Sertoli cell proliferation,
     but no cell maturation or sperm production, because Sertoli cells don’t express AR until age 5 years,
     so there’s no intratesticular paracrine T action.

3. Puberty – completion of germ cell proliferation + differentiation
   - FSH & paracrine T induce germ & Sertoli cell maturation,
     seminiferous tubule formation & spermatogenesis.
Cells of the testis

- Late spermatid
- Early spermatid
- Meiosis
- Basal lamina
- Fibroblast
- Cytoplasmic bridges
- Secondary spermatocytes
- Primary spermatocyte
- Spermatogonium
- Interstitial cells
- Leydig cells
- Inhibin
- FSH
- LH
- T (testosterone)

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Pathobiology of CHH

normal adult male

TV: 25 mL  T: 22 nmol/L

mature testes

male with severe CHH

TV: 2 mL  T: <1.0 nmol/L

immature testes

Kumar, 2006
Spermatogenesis-induction in CHH
GnRH pump therapy in Congenital HH

- Beautiful Endocrinology = replace the missing hormone
- GnRH: delivered as s/c 120 min pulses via minipump.
  - physiologically elegant.
  - has even been used to induce normal puberty.
- BUT
  - needs to be used continuously.
  - doesn't work in pituitary disease.
  - unavailable in many countries & unnecessarily expensive

Lutrelef® disposable microinfusion device

$1000
Gonadotropin therapy in HH to induce Spermatogenesis

- FSH (hMG, rFSH, or corifollitropin-alpha):
  1. Sertoli and germ cell proliferation.
  2. + umolar T → testicular growth & spermatogenesis.

- hCG (LH T1/2 is too short):
  1. T secretion by Leydig cells
  2. Endocrine (nmol/L) systemic effects
  3. Paracrine (μmol/L) effect in testes:
     2. Paracrine T action = Sertoli & germ cell differentiation.

Always check the dose

siempre revise que el número que aparezca sea el tamaño de la dosis recomendada 250.
How likely is sperm-induction to succeed in Hypog Hypog?
Final TV in CHH men after pulsatile GnRH (hCG + FSH) therapy

Pitteloud, JCEM 2002
Sperm outcomes of CHH men on GnRH or hCG+FSH therapy

- TV >4 mL: 80%
- TV <4 mL: 50%
- Bilaterally cryptorchid: 30%

Pitteloud, 2002; Liu, 2009; Burris, 1998; Miyagawa, 2005; Büchter, 1998

3 - 7 injections/week
duration 1-3 years
Fertility Outcome in CHH: maximal sperm count

\[10 \text{Lg} \left( \text{Sperm Count} \times 10^6/\text{mL} \right)\]

<table>
<thead>
<tr>
<th>Absent puberty</th>
<th>Partial puberty</th>
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<tbody>
<tr>
<td>TV ≤ 4 mL</td>
<td>TV &gt; 4 mL</td>
</tr>
<tr>
<td>n = 32</td>
<td>n = 19</td>
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</tbody>
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Azoospermic: n = 9

Pitteloud, JCEM, 2002
Predicting Success & Rationalising Failure

Pre-treatment predictors for success:

- adult-onset HH, *so minipuberty & puberty occurred.*
- CHH with pre-treatment TV $>4mL = h/o$ partial puberty.
- not cryptorchid, so no therapeutic or surgical trauma – potentially milder neuroendocrine defect
- higher baseline Inhibin B level.
- not harbouring KAL1 mutation (X-KS)

Sperm count may remain low, but:

- CHH men can be fertile with counts $<2x10^6/mL$
- & ICSI is becoming more widely available.
Why does gonadotropin replacement take so long to work in CHH men (compared with women) & why isn't it more successful?

1. Absent minipuberty?
2. Flawed gonadotropin regime?

Neonatal gonadotropin therapy in male congenital hypogonadotropic hypogonadism

Claire Bouvattier, Luigi Malone, Jérôme Bouligand, Catherine Dodé, Anne Guilochnon-Mantel and Jacques Young

Abstract | Congenital hypogonadotropic hypogonadism (CHH) causes pubertal failure and infertility in both women and men due to partial or total secretory failure of the two pituitary gonadotropins lutropin (LH) and follicitropin (FSH) during periods of physiological activation of the gonadotropic axis. Men and women with CHH frequently seek treatment for infertility after hypogonadism therapy. Some etiologies, such as autosomal dominant or X-linked Kallmann syndrome, raise the question of hereditary transmission, leading to increasing demands for genetic counseling and monitoring of medically assisted pregnancies. Diagnosis and treatment of newborn boys is, therefore, becoming an increasingly important issue. In male individuals with complete forms of CHH, the antenatal and neonatal gonadotropin deficit leads to formation of a micropenis and cryptorchidism, which could undermine future sexual and reproductive functions. Standard treatments, usually started after the age of puberty, often only partially correct the genital abnormalities and spermatogenesis. The aim of this Review is to examine the possible additional benefits of neonatal gonadotropin therapy in male patients with CHH. Encouraging results of neonatal therapy, together with a few reports of prepubertal treatment, support the use of this novel therapeutic strategy aimed at improving sexual and reproductive functions in adulthood.
Study of Optimal timing of FSH therapy

### Treatment

**CHH Men**
- prepubertal testes (TV <4 mL)
- no prior gonadotropins
- no cryptorchidism

- **n=6**
  - no pre-treatment
  - GnRH (24 M) [LH + FSH]

- **n=7**
  - rFSH Gonal-F (4 M)
  - GnRH (24 M) [LH + FSH]

### Monitoring

- FSH, T & E₂ levels
- 12hr LH frequent sampling
- Testis ultrasound
- Testis biopsy

**Regular monitoring to ensure**
- normal range T & E₂
- FSH 4-6 IU/L.

**Study endpoints:** TV & Sperm count

*Dwyer, JCEM 2013*
Effects of 4 months r-hFSH pre-treatment

Baseline
1.1 ±0.2 mL

TV doubled (p<0.005)

Post-4M rFSH
2.2 ±0.3 mL

immature Sertoli cells, primitive spermatogonia, absent Leydig cells, small seminiferous tubules

Spermatogonia deploying to basement membrane. Ratio of Germ:Sertoli cells doubled

Further maturation after 4 months
GnRH-pulse Rx
## Testicular Volume & Sperm Outcomes

At study completion, the rFSH pre-treated group had:

<table>
<thead>
<tr>
<th></th>
<th>10 ±4  vs.  7 ±3 mL  [p=0.06]</th>
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<tbody>
<tr>
<td>Larger TV</td>
<td></td>
</tr>
<tr>
<td>Higher % men with sperm</td>
<td>7/7   vs.  4/6</td>
</tr>
<tr>
<td>Higher max. sperm counts</td>
<td>(x10⁶/mL)</td>
</tr>
<tr>
<td>mean:</td>
<td>35 ±20 vs. 17 ±10</td>
</tr>
<tr>
<td>range:</td>
<td>10–80 vs. 0–70</td>
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When to introduce FSH for spermatogenesis-induction in HH?

“Classical” hCG-first regimens based on:

1. FSH = expensive ($20 per 75 IU Amp) & hCG = cheap.
2. Fertility may be achieved with hCG-monotherapy.
3. Pharma licensing studies of FSH-products excluded
   - men who achieved sperm on titrated hCG monotherapy.
   - men who failed to normalise serum T on hCG alone.

1 AACE guidance
2 eg. Serono 5844; MK 8962
FSH before hCG in severe CHH?

“Logical” Regime for CHH men with TV ≤4 mL

- FSH to maximise the no. of spermatogonia & immature Sertoli cells, before causing them to differentiate through exposure to hCG-induced paracrine-T.
- Meanwhile continue exogenous endocrine T therapy.
- Titrate FSH dose to achieve serum levels 4-8 IU/L. *
- After 2-3 months, replace T with hCG & continue FSH.
- Titrate hCG to achieve normal FBC, T & E₂ levels.

…and for CHH men with TV >4 mL?

- start FSH & hCG simultaneously.

* pre-study meta-analysis for MK8962
Clinical Case

Presented with absent puberty & CHH aged 19

- started on Nebido 1g every 4 months $^{1,2}$.
- L testis $2\,mL$ & scheduled for R orchidopexy.
- Urologist asked me to make his testes bigger, so as to make surgery technically easier.
  - started FSH 75 $IU$ daily & no further Nebido.
  - after 3 months, added hCG 1,500 $IU$ 2x/week.
  - achieved target range Testo, $E_2$, FSH & FBC.
  - 6 months later: both testes $8+6\,mL$ in scrotum.
  - declined offer to continue FSH+hCG ± bank sperm.

- Minipuberty?

1. Santhakumar, Clinical Endocrinology, 2012
2. Pazderska, Endocrine Connections, 2017
Improving Sperm Outcomes in CHH

- Diagnose absent minipuberty in B/L cryptorchid boys & treat with FSH+hCG – may obviate need for orchidopexy.
- Ensure CHH men are aware of fertility options & signpost to specialist centre while their partners are still young.
- Genetic counselling to couples: 5-10% risk of transmission.
- Appropriate sequence of gonadotropin initiation – hCG-alone is pointless in CHH.
- Adjust FSH dose to maintain serum FSH 4-8 IU/L
- Adjust hCG dose to achieve normal serum Hb+Hct, T & E₂.
- Don’t give up until >2 years FSH+hCG / GnRH, but plan for early ICSI ± mTESE if older partner, & for sperm banking.
- Screen offspring for minipuberty at 1-3 months.
Thank you for your attention.