Hypogonadism/Infertility Case studies – Evaluation and treatment

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Presentation

• 2 cases
• Interactive
• Evaluation
• Monitoring
• Treatment
• Discussion about fertility
Case 1

• 33 year old Male Malay
• Presented age 25 - 2002
• Delayed secondary sexual characteristics – minimal axillary hair, small penis, testes, bilateral gynecomastia,
• Lack of early morning erection
• No history of tiredness / blurred vision
On examination

- Normotensive (BP 110/70)
- Weight 74.8kg, Height 160.7 cm, BMI 29
- Childlike voice
- Gynaecomastia
- Minimal axillary hair, Tanner A 1 P 2
- Small testes 3 mls
- Small penis (< 1 cm)
Investigations

- 9am testosterone 2.8 nmol/L (8-30)
- LH 37 U/l, FSH 30.1 U/l
- Prolactin - 96 mIU/L
- 9 am cortisol - 374 nmol/L
- T4 13.19 pmol/L
- TSH 1.3 mU/L
Diagnosis

- Primary hypogonadism
- Chromosomal analysis
  - 47 XXY, compatible with Klinefelter’s syndrome
  - MRI pituitary – small pituitary, no mass lesion seen
Treatment

- Started on testosterone enanthate 250 mg 4 weekly
- Early morning erection restored
- Bigger testicle size
- Libido good
- Voice – deeper
Progress - 2004

- Married in 2004
- Desires to have child
- Good libido
- Counseled on child adoption
- Testes 3 mls bilaterally
2005-2011

- Yearly follow up
- weight gain of up to 20 kg
- Libido ok
- LH/FSH $\Rightarrow$ between 1-4 generally
- Testo trough (latest) 4.4
- Visits a fertility centre – told slim chance of getting wife pregnant (unclear whether had work up)
Questions

• What are the signs and symptoms of hypogonadism?
• What are the laboratory tests to perform?
• What are the imaging modalities needed?
• What are the treatment options?
• What are the chances of fertility?
# Signs and symptoms

<table>
<thead>
<tr>
<th>Specific</th>
<th>Non-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased libido</td>
<td>Decreased energy, motivation, self-confidence</td>
</tr>
<tr>
<td>Incomplete sexual development</td>
<td></td>
</tr>
<tr>
<td>Loss of body hair</td>
<td>Sad</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Poor memory/ concentration</td>
</tr>
<tr>
<td>Small shrunken testis</td>
<td>Reduced muscle bulk</td>
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<tr>
<td>Infertile</td>
<td>Anemia</td>
</tr>
<tr>
<td>Hot flushes, sweats (? Andropause)</td>
<td>Increase in body fat</td>
</tr>
<tr>
<td></td>
<td>Reduced work performance</td>
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</tbody>
</table>
Testosterone

Free T = unbound T
Bioavailable = unbound + albumin bound
The decline in total testosterone (T) level is evident from the age of 45–50 years. Free (bioavailable) testosterone starts to decline even earlier due to increasing levels of sex hormone-binding globulin (SHBG) which binds tightly to testosterone.

Data from Vermeulen A. 1993 Annals of Medicine 25:531-4
Investigations

- Testosterone (Early morning)
- LFT’s, sHBG [http://www.issam.ch/freetesto.htm]
- Free testosterone (Calculated)
- LH/FSH
- Prolactin
- Iron studies
- Semen analysis
- DEXA bone scan
- Genetic testing

?hypogonad

Cause and target organ damage
Imaging

MRI pituitary

Ultrasound testes
Algorithm

History and physical (symptoms and signs)

Morning Total T

- Normal T

- Low T #

Exclude reversible illness, drugs, nutritional deficiency
Repeat T [use free or bioavailable T, if suspect altered SHBG^]
LH+FSH
SFA [If fertility issue]

Confirmed low T [Low total T; or free or bioavailable T]

- Low T, low or normal LH+FSH (secondary hypogonadism)
  - Prolactin, iron, other pituitary hormones, MRI [under certain circumstances*]

- Low T, high LH+FSH (primary hypogonadism)
  - Karyotype [Klinefelter syndrome]

- Normal T, LH+FSH

Follow up
Indications for treatment

• Symptomatic men with androgen deficiency syndrome
• Aims are to induce and maintain secondary sexual characteristics
• Improving sexual function
• Improving bone health
• Improve ‘psychological’ aspect – well-being, self confidence
Contra-indications

Absolute

• Breast cancer
• Prostate cancer
• Hct > 50%
• Untreated severe obstructive sleep apnea
• Severe lower urinary tract symptoms
• Severe heart failure
• Those desiring fertility

Relative

• Palpable prostate nodule
• PSA > 4 ng/ml
  -> needs further urological evaluation before testosterone replacement can be considered
Methods of replacement
Injection

• Most commonly used
• Common forms – testosterone enanthate (sustanon)
• 3-4 weekly injections
• Testosterone levels rise to ‘supraphysiological’ range after 3-4 days and gradually declines in 1-2 weeks
• Corrects symptoms and relatively inexpensive, can be self administered
• Newer form – testosterone undecanoate (Nebido) -> much more expensive -> but only needs to be given once every 12 weeks
Orals

• Not commonly used
• Variable clinical response
• Metabolized in liver -> risk of liver related problems – adenoma, hepatotoxicity
• Multiple daily dosing may be required
Topical

- Testosterone gels
- Buccal testosterone
- Testosterone patches
- Not commonly used in Malaysia
- Problems all relate to the area of use
Monitoring

- Evaluate patient 3-6 months after starting therapy – monitor sx, side effects
- Monitor testo levels – normally if injection, midway between injections, if levels too high, then need to adjust frequency
- Safety profile, check Hct, PSA, perform digital rectal exam annually
- Check topical areas – buccal, injection sites, patch sites etc..
Case 2
History

• Male, aged 17
• In 2007, aged 14, presented to the endocrinologist with delayed puberty
• Cleft palate/lip repair aged 2
• Parents noted small genitalia
• Short stature
• Unable to smell certain food
• Previously undescended testes – with orchidopexy aged 13
On examination

- Small testes 2 mls bilaterally
- Mildly dysmorphic facial features
- Weight 44.3 kg, Height 147.5 cm BMI 20.2
- Dysmorphic facial features
- Tanner 2 axilla/pubic hair
Investigations

- Testosterone 0.6 nmol/L
- GH 0.2 mU/L (0.2-13)
- IGF 44.3 ng/ml (low)
- TSH 2.86
- Prolactin 6.1 ug/L (1.4-24.2)
- FSH 0.7, LH 1.0
- 9 am cortisol 577 nmol/L
Diagnosis

- Hypogonadotrophic hypogonadism – likely to be Kallmann’s syndrome
Treatment

• Started on Testosterone enanthate 125 mg im, 2 weekly then 3 weekly
Progress

- Discontinued testosterone 125 – due to financial constraints
- Seen in the public facility, restarted testosterone enanthate at 50 mg 4 weekly
- Peak testo 5.76
- Weight increased, voice hoarse, penis lengthened
- Testes 2 mls bilaterally
- Testosterone stopped temporarily for GH axis assessment
Further investigations - ITT

- Adequate hypoglycemia
- Peak GH response 1.54 (inadequate)
- Peak cortisol response 619.6 nmol/L
- Height 153 cm (10-25<sup>th</sup> centile)
- MRI – no pituitary abnormalities – no mention of olfactory bulbs
- Bone age – in keeping with chronological age
2008

- Testo < 0.7, FSH 0.81, LH 0.69
- IGF 1 76.1 ug/ml (220-972)
- Testosterone enanthate restarted at 50 mg im monthly
2009-2011

- Testosterone increased to full dose 250 mg 4 weekly
- Normal karyotype – on chromosomal analysis
- Weight has increased 11 kg for 3 years
- Height increased 7 cm \( (50^{th} \text{ centile}) \)
- Tanner Stage 2 genitals/axilla
- Testes 2 mls bilaterally
- Trough testosterone 6.24, FSH 0.81, LH 0.81
Issues

- ? Testosterone replacement adequate
- Mother asks about fertility issues
- ?? GH replacement
Semen analysis (normal)

- Volume > 2.0 mls
- Viscosity – normal
- pH 7.2-8.1
- Sperm concentration > 20 million/ml
- Motility %, Total > 50%, Rapid progressive > 25%
- Morphology
- Vitality, ( % live/dead)
- Direct sperm antibody - Negative
- Nucleated / round cells < 1 millions/ml
- Leucocytes per ul - < 25-75

→ ? International consensus for infertility?

<table>
<thead>
<tr>
<th>Sample Semen Analysis Report – John SMITH DOB 2/10/73</th>
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<tbody>
<tr>
<td><strong>Patient Value</strong></td>
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<tr>
<td>-------------------</td>
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<tr>
<td>Partner’s name</td>
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<tr>
<td>Date of sample</td>
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<tr>
<td>Duration of abstinence (days)</td>
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<tr>
<td>Difficulty in producing</td>
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<tr>
<td>Was all the sample collected?</td>
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<tr>
<td>Interval between ejaculation and start of analysis (min)</td>
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<tr>
<td>Volume (ml)</td>
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<tr>
<td>Appearance</td>
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<tr>
<td>Liquidation</td>
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<tr>
<td>Viscosity</td>
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<tr>
<td>pH</td>
</tr>
<tr>
<td>Debris</td>
</tr>
<tr>
<td>Agglutination</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>Motility (%)</td>
</tr>
<tr>
<td>(a) rapid progression</td>
</tr>
<tr>
<td>(b) slow progression</td>
</tr>
<tr>
<td>(c) non-progressive</td>
</tr>
<tr>
<td>(d) immotile</td>
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<tr>
<td>Vitality (%)</td>
</tr>
<tr>
<td>Other Cells (x 10^5/ml):</td>
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<tr>
<td>Round cells</td>
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<tr>
<td>White blood cells</td>
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<tr>
<td>Antisperm Antibodies (% bound):</td>
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<tr>
<td>MAB test for IgA</td>
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<tr>
<td>Location</td>
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<tr>
<td>MAB test for IgG</td>
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<tr>
<td>Location</td>
</tr>
<tr>
<td>Concentration (x 10^7/ml):</td>
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<tr>
<td>Count/ml</td>
</tr>
<tr>
<td>Total count in ejaculate</td>
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<tr>
<td>Morphology (%)</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Abnormal</td>
</tr>
<tr>
<td>Head defects</td>
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<tr>
<td>Midpiece defects</td>
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<tr>
<td>Tail defects</td>
</tr>
<tr>
<td>Cytoplasmic droplets</td>
</tr>
<tr>
<td>Teratospermia index (TZI)</td>
</tr>
<tr>
<td>Comment</td>
</tr>
</tbody>
</table>

**Notes:** This report does not give any information about the integrity of the sperm DNA. DNA fragmentation levels are now considered to be more reliable than conventional semen parameters in assessing male fertility. This sample has been cryopreserved and will be stored for 4 weeks. To request sperm DNA fragmentation as an additional test, please telephone TDL Andrology on 0207 307 7312.
Testicular biopsy – TB

• For those who have azoospermia, TB is performed to determine if a blockage is present or the cause of the infertility is due to the primary cause
• Present in 5-10% of men evaluated in infertility
• 2 sequential sperm counts < 20 million sperm /mls of seminal fluid
• May not be indicated if the cause is clear cut such as Klinefelter’s
• As a method to retrieve sperm to facilitate IVF or ICSI (just 1 single viable, sperm needed per oocyte)
TB - Method

- Local anaesthesia
- Small piece of tissue removed from testes
- Then, pathologist interprets the findings
- Report will include severity of testicular abnormality, findings ‘homogenous’ or ‘heterogenous’ and mature spermatids
- E.g. – sperm retrieval will be low if a pathological diagnosis of “maturation arrest identified with only primary spermatocytes present in all tubular profiles”
Fertility induction in Hypogonatrophic Hypogonadism (1)

- Stop regular testosterone
- HCG 1500 i.u. injected subcutaneously twice a week for 6 months
- Measure testosterone every 8 weeks, if testosterone > upper limit of normal, half dose of HCG
- Sperm count after 6 months
Fertility induction (2)

- If azoospermic, LH 75 U and 75 U FSH injections added. FSH – stimulates spermatogenesis
- HCG dose remains the same
- Continue to check testosterone every 2 months
- Dose of both LH/FSH injections and HCG injections can be halved if testo > upper limit of normal
- Recheck sperm counts after 3 and 6 months of combination treatment
- Combination dose can be continued for up to 18 months
- FSH should increase testicular volume > 10 mls, up to 1 yr
- Pure FSH injections are also possible – main setback – cost
- Sperm freezing
1st case

- 10% Klinefelter’s syndrome – mosaic form – presence of sperm of ejaculate and subsequent paternities – offer genetic testing to confirm hypergonadotrophic hypogonadism
- Non-mosaic forms – azoospermia – Infertile
- Spontaneous conception of Klinefelter’s patient in 1982 (non-mosaic), up to 8.4% of non-mosaic ones – viable sperm found
- If not, then Testicular sperm extraction with ICSI (success rates range from 16-60% for TESE)
- Risk of genetic transmission of inherent problems – preimplantation genetic diagnosis
- To date 101 genetic children born to Klinefelter’s syndrome patients with reproductive assistance, 2 born with spontaneous conception
2nd case

- Start with HCG injections
- Then, add LH/FSH injections
- Consider gonatrophin pump (GnRH pump)
- 3 monthly testosterone, sperm count
- Duration of use of up to 18 months
- Success rates will depend on testicular volume, and prior use of androgen therapy
Gonadotrophin Pump

- GnRH produced by hypothalamus and released in pulsatile manner
- Pump works on the same principle – short bursts 90-120 minutes intervals
- Needle inserted below skin, ampoule changed every 10 days
Thank you

Questions?