Approach to the infertile couple and male factor infertility

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Monash University.

ESA Seminar May 3rd-5th 2019, Perth.
Outline of Presentation

Overview of male factor infertility

Assessment of a man presenting with infertility / subfertility
  Infertility as a marker of male health

Hypogonadotrophic hypogonadism
  Androgen abuse
  Induction of spermatogenesis

Semen Analysis

Klinefelter syndrome
  Evolving fertility considerations
Infertility

Inability of a couple to conceive after 12 months of regular sexual intercourse without the use of contraception (WHO)

6 months for women aged ≥ 35 years (ASRM)

80-90% of apparently ‘normal’ couples will conceive within 12 months

95% will conceive within 24 months

Fecundability decreases over time and with increasing age of the female partner

Affects approximately 8-12% of couples worldwide

Male factors are solely responsible in 20-30% and contribute to 50% of cases overall

Approximately 7% of men are infertile
Couples with Infertility

Intercourse timing, frequency and adequacy

Timing and Frequency
Every second day around time of ovulation
2-3 times weekly throughout cycle

Erectile function
Erectile dysfunction
Ejaculatory difficulties – premature; retrograde

Age of female partner

Menstrual cycle
Ovulatory cycles
Couples with Infertility: Case Report

2015: 46 year old man referred by urologist with (R) testicular atrophy / low Te following (R) hydrocele repair 2 years

Wife aged 36 yrs; 4 yr old son spontaneously conceived
TV: 6 ml (R) and 15 ml (L)
Te 6.6, 7.3 nmol/L; LH 7.8 IU/L; FSH 14.2 IU/L
SA 5 x 10 million/mL with ↑ abn forms and ↓ motility
Low libido; ED - responsive to PDE5-inhibitors
(R) C4/5; C5/6 canal stenosis awaiting surgery
Advised to avoid testosterone therapy
Referred for assisted conception

2019: 41 year old woman referred for ‘discussion about fertility’
Did not feel comfortable with fertility specialist
Wanted to try natural alternatives - unsuccessful
Husband now had severe ED and non-existent libido
- adverse reaction to Cialis
Causes of Male Factor Infertility

Endocrine <1%
  Gonadotrophin deficiency
    • congenital
      Kallmann’s Syndrome
    • acquired
      hyperprolactinaemia
      pituitary tumours
      TSS/pituitary radiotherapy

Exogenous androgens
Causes of Male Factor Infertility

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Exogenous androgens

Spermatogenesis 60%
- Idiopathic → genetic
- Congenital
  - Klinefelter Syndrome
- Acquired
  - drugs, toxins
  - infection

Obstruction 30%
- Congenital
  - BCAV
- Acquired
  - vasectomy
  - STI

Intercourse
- Erectile
- Ejaculatory
- Anatomical
- Psychosexual

Sperm antibodies
Assessment of Male Factor Infertility

Scrotal examination
Testicular size
Varicocele
Bilateral Congenital Absence of the Vas (BCAV)
  Forme fruste of Cystic Fibrosis
    – 50-75% have CFTR gene mutation
    – genetic counselling

Hormonal profile
Testosterone (SHBG, cFT); LH; FSH; PRL
  FSH is a predictor of spermatogenesis
  consensus reference interval for FSH (1.3–8.4 IU/liter)

Semen analysis
Correct protocol: 2 - 7 days of abstinence
Need for repeated samples – spun sample
Assessment of Male Factor Infertility

Scrotal examination

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Male Infertility as a Window to Men’s Health

1. Diagnosis of related medical conditions

- Testicular volume - Klinefelter Syndrome
- Vas Deferens - Cystic Fibrosis
- Testicular Adrenal Rests - Congenital Adrenal Hyperplasia
- Erectile difficulties – Diabetes Mellitus

Windows of opportunity: a holistic approach to men’s health.
Male Infertility as a Window to Men’s Health

1. Diagnosis of related medical conditions
   - Testicular volume - Klinefelter Syndrome
   - Vas Deferens - Cystic Fibrosis
   - Testicular Adrenal Rests - CAH
   - Erectile difficulties – DM

2. Infertility predicts testosterone deficiency

357 severely oligospermic men
12% had Te < 2.5 percentile

Andersson et al. JCEM 89:3161-67;2004

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Male Infertility as a Window to Men’s Health

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   - Erectile difficulties – DM

2. Infertility predicts testosterone deficiency

3. Link with testicular cancer
   Potential increased risk of developing testicular cancer: 4-10-fold ↑ with undescended testes.

Windows of opportunity: a holistic approach to men’s health.
Male Infertility - Voodoo and Witchcraft

Boxers versus briefs
Saunas and spas
Supplements
- Folic acid and Zinc
- Omega-3 and omega-6 fatty acids
- Anti-oxidants (selenium, Vit C, Vit E, glutathione, coenzyme Q10, L-carnitine)
- Fenugreek
- Ashwagandha (Indian ginseng)
- Avoid phytoestrogens

Aurora Borealis (Northern Lights)

Festival of the Steel Phallus (Kanamara Matsuri)
Empiric Treatment of Male Infertility

Clomiphene citrate (off-label)
- racemic mixture of 2 isoforms
  - enclomiphene (antagonist)
  - zuclomiphene (agonist / antagonist)

- **Idiopathic infertility**
  - American Urological Association (2012)
    - Most prescribed empiric medical therapy

- **Low Te / (N) LH**
  - Rationale – optimise Te without compromising spermatogenesis

Side-effects (generally well tolerated)
- GI, dizziness, hair loss, gynaecomastia
- 1.5% incidence of reversible visual disturbance


**Idiopathic infertility**

Meta-analysis 11 trials
- clomiphene 50 mg or tamoxifen
- ↑ pregnancy rates
  - OR 2.42 (95% CI 1.47-3.94)
- sperm concentration and motility modestly ↑WMD* 5.24million/mL (95% CI 2.12-8.37)
  - *weighted mean difference (WMD)


Meta-analysis 3 studies - min 25 mg clomiphene 2nd daily x 3 months
- ↑ 7.7 million sperm per mL
Empiric Treatment of Male Infertility

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**Aromatase Inhibitors**
- Role in low T:E ratio men?
  - Obese men do NOT have a better response rate

Idiopathic infertility

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Androgen Abuse / Misuse

“Statistics”

Cosmetic as well as athletic improvements
15% contamination of 'dietary supplements’
50% non-disclosure of usage

7% of UK men seeking infertility treatment (2000 - 2011) were receiving testosterone therapy

Clues to usage

Physique; +/- testicular atrophy
Low Te
   undetectable gonadotrophins
   very low SHBG
Elevated Hb /hct
Adverse lipid profile

Recovery of Spermatogenesis after Exogenous Androgens

WHO Contraceptive Data

Weekly IM injection of 200 mg T enanthate.

Cessation of IMTE → 84% achieved >20x10^6/mL after median 3.7 months BUT only 46% returned to baseline value

Probability based recovery rate after male hormonal contraception

Multivariate analysis based on 30 studies: >20x10^6/mL

- 67% at 6 months
- 90% at 12 months
- 96% at 18 months
- 100% at 24 months

Liu et al. Lancet 2006;367:1412

Narayana #7459 ENDO 2019

Androgen abusers took 316 days to return to the median sperm concentration of non-androgen abusers when they ceased using
Gonadotrophin Therapy for Hypogonadotrophic Hypogonadism

hcg
- Serum half-life 36 hours
- Increased receptor activity and half-life cf. to LH
- Decreasing sperm counts after 12/12 of monotherapy

rFSH
- Ineffective as monotherapy
- Requires a rise in intra-testicular testosterone

Combined gonadotrophin therapy
- Equivalent clinical efficacy to GnRH
- More convenient
Induction of Spermatogenesis in Gonadotrophin Deficient Men

Protocol

hCG 1500 IU sc twice weekly

azospermia at 6/12 →

FSH 75 IU sc thrice weekly

(modal dose 150 IU x3/wk)

Median time to first sperm: 7.1 months

Median time to conception: 28.2 months

Median sperm conc. for spontaneous pregnancy was 8x10^6/ml

Liu et al. JCEM 2009, 94:1801-808

<table>
<thead>
<tr>
<th>Andrology Test Name</th>
<th>Pathology Fee</th>
<th>Medicare Rebate</th>
<th>Out of Pocket Cost</th>
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<td>SEMEN FREEZE FEE</td>
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<td>MONASH IVF STORAGE /6MTHS</td>
<td>$200.00</td>
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<td>$200.00</td>
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Monash IVF Costs
Induction of Spermatogenesis in Gonadotrophin Deficient Men

Predictors of Response

Testis volume
Total volume 20mls – baseline or after Rx – increases pregnancy rate 2- to 3-fold

Prior gonadotrophin therapy
Second treatment cycle results in 2- to 3-fold more rapid spermatogenesis

Lack of previous androgen Rx

Non-IVF pregnancies occurred at a median sperm concentration of 8 M/ml after 2.3 yr treatment

Liu et al. JCEM 2009, 94:801-808

Table 2. Baseline participant and treatment emergent characteristics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sydney and Melbourne (n = 75 men)</th>
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<tr>
<td>Diagnosis</td>
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<td>IHH</td>
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<td>Kallmann</td>
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<td>Pituitary</td>
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<td>No</td>
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<td>Yes (female factor)</td>
<td>20</td>
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<td>Yes (other)</td>
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<tr>
<td>Age (yr)</td>
<td>34 ± 1</td>
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<tr>
<td>Partner’s age (yr)</td>
<td>29 ± 1</td>
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<td>Initial sum testis volume (ml)</td>
<td>13 ± 1</td>
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<tr>
<td>Treatment duration (month)</td>
<td>23 ± 2</td>
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<tr>
<td>Treatment duration with hCG alone (month)</td>
<td>5 ± 1</td>
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Values are expressed as total number or mean ± sem. Individual sums may not total 75 due to incomplete data.

38 pregnancies
Induction of Spermatogenesis in Gonadotrophin Deficient Men

<table>
<thead>
<tr>
<th>Study and Author</th>
<th>HCG dose (IU)</th>
<th>Dose frequency (per week)</th>
<th>FSH dose (IU)</th>
<th>Dose frequency (per week)</th>
<th>Number of patients (n)</th>
<th>Duration (months)</th>
<th>Spermatogenesis recovery (%)</th>
<th>Pregnancy rate (%)</th>
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<tr>
<td>Burger and Baker 1984</td>
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IU: international unit; HCG: human chorionic gonadotropin; FSH: follicle-stimulating hormone

**PREGNYL**
gonadotrophin chorionic human 1500 units injection [3 ampoules]

**NB: Authority 3x3 with 5 repeats**

Restricted Benefit: Infertility.
Clinical criteria: The condition must be due to HH.
Population criteria: Patient must be male.

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**PUREGON**

follitropin beta 900 units/1.08 mL injection.

1 and 5 repeats

Restricted Benefit: Infertility

Clinical criteria: The condition must be due to HH AND The treatment must be following failure of 6 months' treatment with hcg to achieve adequate spermatogenesis, AND The treatment must be administered with hcg
Semen Analysis

Sperm conc. <10 million per mL → karyotype
Sperm conc. <5 million per mL → Y- chromosome microdeletion

Present in 10-18%
May be transmitted by ICSI (first pregnancy 1992)


NB: 5-6% of infertile men have a chromosomal abnormality

Azospermia

10 - 15% of azoospermic men have Klinefelter syndrome
(low/low-normal Te; ↑↑FSH)

Herlihy AS et al.
The prevalence and diagnosis rates of Klinefelter syndrome: an Australian comparison.
Semen Analysis

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Azospermia

Obstructive (vasectomy) (N) Te, LH, FSH
Testicular Biopsy
  ➤ ICSI
Spermatogenic Failure ↓Te; ↑LH, ↑FSH
  ➤ Donor Sperm
    Limited no. of donations (5-10)
  ➤ Adoption
Fertility in Non-Mosaic Klinefelter Syndrome

Successful recovery of spermatozoa by TESE first reported in 1996


First pregnancy by TESE/ICSI reported in 1998

_Palermo GD et al. NEJM 1998; 338:588-590._

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Sperm recovery and ICSI outcomes in Klinefelter syndrome: a systematic review and meta-analysis

Giovanni Corona¹,†, Alessandro Pizzocaro²,†, Fabio Lanfranco²,†, Andrea Garolla⁴,†, Fiore Pelliccione⁴, Linda Vignozzi⁵, Alberto Ferlin⁴, Carlo Foresta⁴, Emmanuele A. Jannini⁶, Mario Maggi⁵, Andrea Lenzi⁷, Daniela Pasquali⁸, Sandro Francavilla⁹,*, and On behalf of the Klinefelter ItaliaN Group (KING)

37 trials with 1248 men
Fertility in Non-Mosaic Klinefelter Syndrome

- 37 trials with 1248 men
  - Mean age 30.9 years

Sperm Retrieval Rate
- 44% per TESE cycle
  - NOT affected by age, TV or LH/FSH/Te

Live Birth Rate 43% per ICSI cycle

Overall Live Birth Rate 16% for couples who initiated ART
Sperm Retrieval in Adolescent Males with Klinefelter Syndrome: Medical and Ethical issues  


Workshop on Klinefelter Syndrome (Muenster, Germany, March 10–12, 2016). Roundtable discussion chaired by Professor Eberhard Nieschlag.

Optimal age range for highest SRR is 15–35 years

Consider psychological readiness to focus on fertility

Neurocognitive function

Not possible to identify sub-set of adolescents / young adults with KS who would have higher SRR

Hormone profile, testicular size, number of CAG repeats in AR, parent of origin of the extra X chromosome
Sperm Retrieval in Adolescent Males with Klinefelter Syndrome: Medical and Ethical issues  


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Gonadal micro-mosaicism is common in KS patients with a ‘pure’ 47, XXY karyotype

Therefore, children conceived by sperm harvested through TESE or Micro-TESE are usually euploid.

Is previous TRT, even when withdrawn for ≥ 6 months at the time of TESE or microTESE deleterious for sperm retrieval rates?

Are treatments designed to increase intra-testicular testosterone secretion (hCG, clomiphene, aromatase inhibitors) efficient or not in increasing sperm retrieval rates?
Fertility in the Androgen Clinic

I. Know your patients as people

II. Do no harm

III. Make fertility a part of the KS conversation

IV. Have a TESE/microTESE expert on standby