The General Practice Education Day
HealthEd / Generation Next
November 7th 2015 Perth

Klinefelter's Syndrome:

Lessons from the archetypal male reproductive disorder

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Director, Andrology Australia

Declarations

- Equity interest in Monash IVF

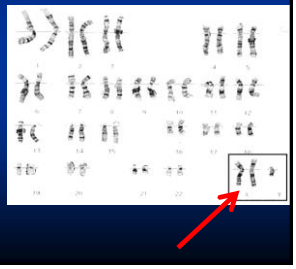
Klinefelter syndrome

"The forgotten syndrome"

Caused by an additional X chromosome

Non mosaic (~90%)
47,XXY

Mosaic & other (~10%)
46,XY/47,XXY
48,XXXY, 49,XXXXY



Klinefelter's Syndrome – 47,XXY

Commonest chromosomal disorder 1:600 males

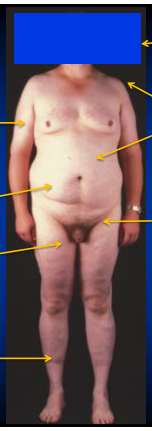
Commonest cause of undiagnosed androgen deficiency

Almost all androgen deficient as adults
- Benefit from replacement

70% escape diagnosis lifelong *Bojesen JCEM 2003*

If it so common and important ..why is this so?

Classical KS in textbooks



Profound learning difficulties
narrow shoulders
gynecomastia
reduced body hair
abdominal obesity
horizontal pubic hairline
small testicular volume
varicose veins

From: Nieschlag and Behre, 2007

Why are KS detection rates so low?

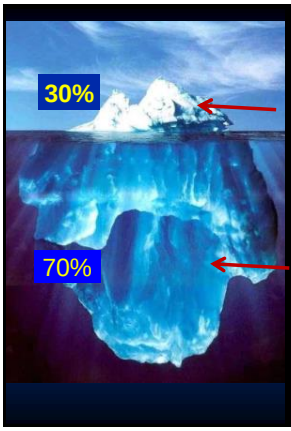
- **Fixation on "classic" phenotype**:
  - Low awareness amongst doctors
  - Routine genital examinations not performed
  - Health literacy of KS men
- Consequence: SIGNIFICANT unmet need
  - EUROPE: 640,000 KS males – 450,000 undiagnosed
  - AUSTRALIA: 16,500 KS males – 11,500 undiagnosed

Natural History of KS

Variability in phenotype

Our experience and perceptions are based on the minority we detected ….. selection bias

Herlihy AS, et al. Genet Med. 2011
Nahata L Clinical Pediatrics. 2013;52(10):936-41
Simpson JL ,Am J Med Genet C Semin Med Genet. 2013;163C(1):64-70



We **know something** about those above the water

We **assume** this tells us about those hidden beneath the waves

Pre-pubertal KS features

Decreased penile size	10-25%
Cryptochordism	27-37%
Delayed speech & motor development	69-75%
Learning difficulties	>75%

Characteristics of developmental profile of KS

(modified from Samango-Sprouse and Rogol, 2002).

Infancy and early childhood	Delay of language
	Dyspraxia: fine/gross motor co-ordination
School-age period	Auditory-verbal memory deficits
	Moderate to severe difficulty in reading skills, writing, spelling, maths

KS psychoneurologic function

NB Data biased by study population

Intelligence

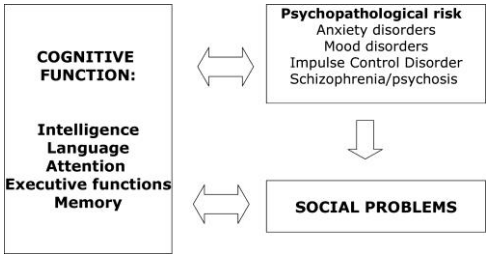
- Overall ~10 IQ point 'shifted to left'
- Most (>80%) fall in the normal range

Specific challenges in some:

- Verbal skills
- Language-based learning difficulties
- Arithmetic
- Executive function

Poorer educational outcomes: primary school → less prestigious careers than siblings

Psychoneurologic function in KS.



Annapia Verri et al. Mol. Hum. Reprod. 2010;16:425-433

Post-pubertal KS - somatic features

- **Infertility (99%)**
- **Small testes (>95%)**
- Decreased testosterone (63-85%)
- Decrease facial and body hair (80%)
- Gynaecomastia (~65%)
- Metabolic syndrome (46%), type 2 diabetes (10-39%)
- Osteopenia (40%) – Osteoporosis ~10%

Gynecomastia in Klinefelter's

Component of 'classic phenotype"
Onset during puberty - *persistent*

Contrast to transient gynecomastia of normal puberty

Incidence ~65% KS cases

Smyth & Bremner 1998 Arch Int Med 158, 1309

Breast cancer in Klinefelter's

- Unilateral lump
- Mean age at diagnosis 58 yrs
- Relatively early metastases

RR 19-30 fold elevated

Brinton et al Breast Cancer Res Treat 2010 119: 185
Swerdlow AJ et at J Natl Cancer Inst 2005: 97, 1204

Breast cancer rates still lower than in women

Co-morbidities in Klinefelter's syndrome

Common:

- Metabolic syndrome, type 2 diabetes
- Circulatory disorders: varicose veins, DVT, PE

Rare:

- Autoimmune diseases: SLE, type 1 diabetes
- Malignancies: breast mediastinal germ cell tumours, lung cancer: non-Hodgkin lymphoma

So what is the current pattern of Klinefelter detection?

Pick up of Klinefelters at/before puberty

Prenatal 21%

- Incidental finding at CVS or amniocentesis
- Non-invasive prenatal testing (NIPT)

Childhood 12%

- Global developmental delay (walking, speech)
- Behavioural or learning difficulties

Puberty 16%

- Incomplete (or perceived delayed) puberty
- Gynaecomastia
- Poor virilisation

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- Incidental finding at CVS or amniocentesis
- Non-invasive prenatal testing (NIPT)

Childhood
- Global d… speech)
- Behavio…

Puberty 1…
- Incompl… (…) …berty
- Gynaecomastia
- Poor virilisation

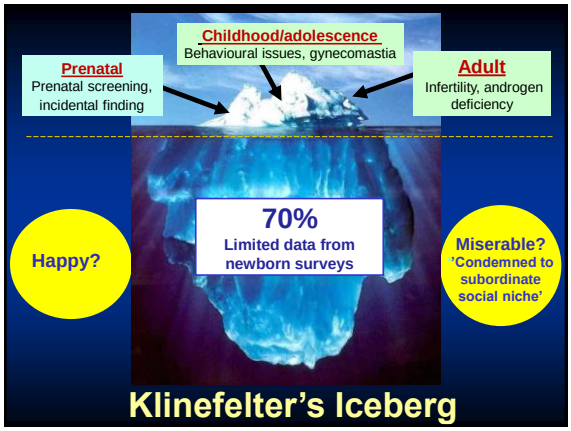
Astute clinician

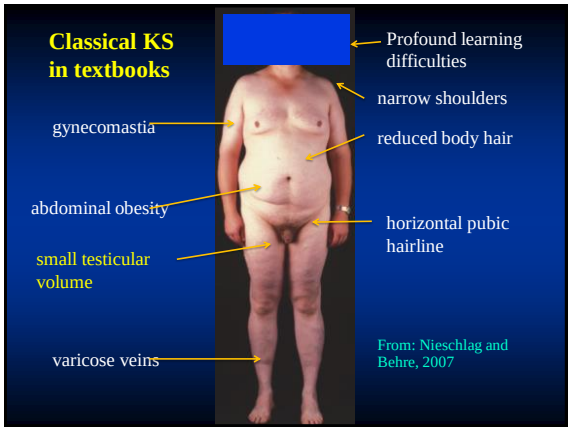
on the look out….

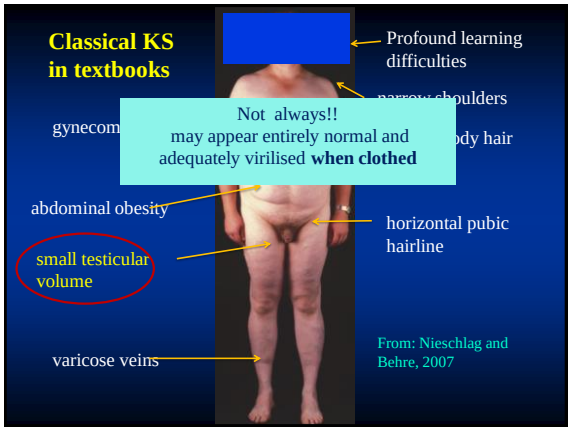
Pick up of Klinefelter's in adulthood- *51%*

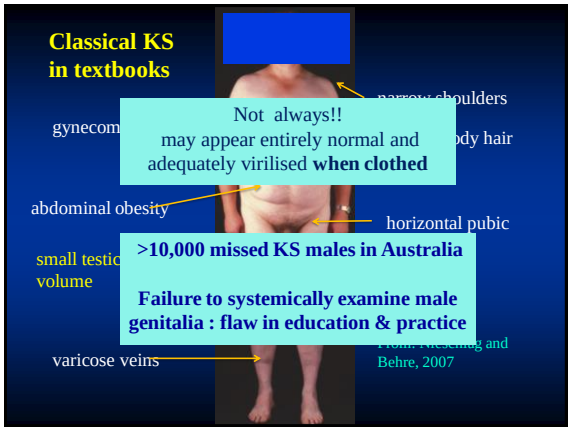
Fertility investigations
- High functioning: partner, employed, full engaged

Androgen deficiency
- e.g. osteoporosis with hip fracture in 60s

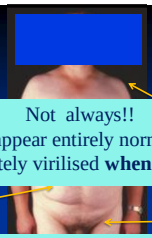








Classical KS in textbooks



narrow shoulders

gynecom

Not always!!
may appear entirely normal and adequately virilised **when clothed**

ody hair

abdominal obesity

horizontal pubic

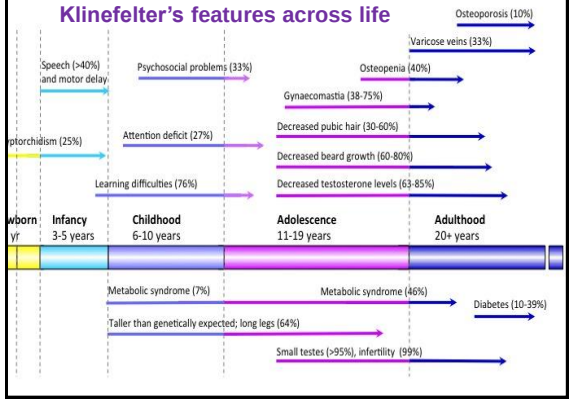
small testicu volume

>10,000 missed KS males in Australia

Failure to systemically examine male genitalia : flaw in education & practice

Klinefelter's syndrome: The most overlooked cause of androgen deficiency. St John B & McLachlan RI Endocrinology Today 2015; 4(1): 8-14

Klinefelter's features across life



Testicular volume: Orchidometer

Diagnosis of KS now often made in fertility clinics

Management issue in Klinefelter's

Support for educational development

If detected early…… assistance for family & boy:

- Counselling
- Support groups
  Australian X and Y Spectrum axys.org.au
- School and post school education
- Physical development
- Support for psychosocial issues

Androgen deficiency

Androgen therapy in physiologically timely fashion

- Pubertal progression → full virilization
- Prevention of gynaecomastia,
- Improved physique, self-esteem, body image
- Bone health
- Body composition and insulin sensitivity

- PBS supportive as definitive example of primary testicular disease at any age

"This explains so much …"
"OK *now* I know what I've been missing'

If you know no better, androgen deficiency symptoms may not be recognised

Only recognise poor quality of life in retrospect

Lifelong sustained benefit from testosterone Rx

Other tests to consider

- Fasting glucose
- Lipids
- TSH

- Bone density
- Vit D

Fertility in Klinefelter's

Commonest cause of testicular failure
14% infertile men with azoospermia

Mr XX
- **Azoospermia**
- **Testes 2ml**
- **FSH 55 IU/L ↑↑↑**
- **Se T 9.2 nM ↓**
- **LH 12 IU/L ↑↑**

'No other complaints really '

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1992
'Donor sperm or adoption..
That's all there is'

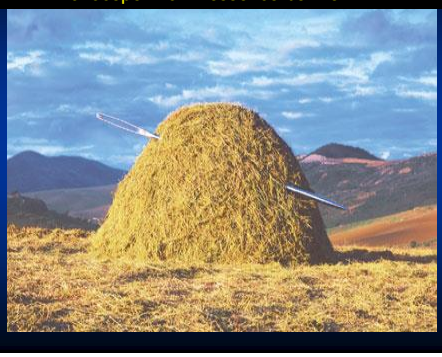
'No other complaints really '

Intracytoplasmic sperm injection (ICSI): 1992

Testis sperm pregnancy rates only marginally poor than other types of infertility

Tubule heterogeneity in spermatogenic failure
'Non-obstructive' azoospermia

Isolating sperm from testicular biopsy
in azoospermia: in essence it's like…….



Prognostic indicators for successful TESE

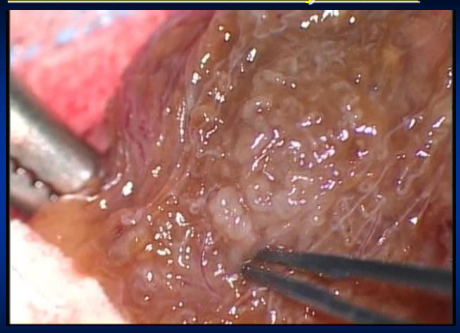
Outlook not related to

PH bilateral cryptorchidism	*Negri Hum Rep 2003*
Prior chemotherapy	*Chan et al Cancer 2001*
Testis volume	
Klinefelters	
Serum FSH	*Zitzmann Hum Reprod 2006*
Serum inhibin B	*Ballesca Hum Rep 2000* *Bohring Fert Steril 2002*

Useful Histology — *Su J Urol 1999 Seo IJA 2001* *Hauser Arch And 2002*

Yq deletion — *Hopps Hum Rep 2003*

Micro-TESE Klinefelter syndrome



32 years FSH 35 IU/L Testes 4 ml

Micro-TESE Klinefelter syndrome

Testicular sperm in ~40% KS

Low risk of abnormal sperm as the stem cell is usually 46, XY

Normal offspring

32 years FSH 35 IU/L Testes 4 ml

Key messages

1. **KS is common: 'classic' stereotype misleading**
2. **Scrotal exam: testis volume 100% sensitivity**
3. **Androgen therapy almost universally indicated**
4. **Fertility possible in >40% → normal offspring**
5. **Genetic screening – NIPT – increasing detection.**

Making the KS diagnosis is life changing

Population-wide screening for Klinefelter's?

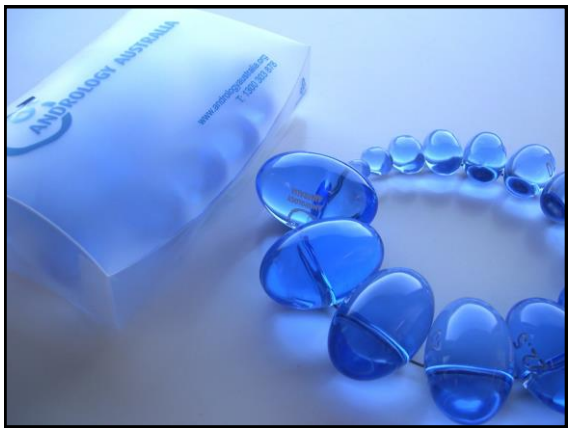
If we knew, what would we do and achieve?

- Risk: benefits
- Cost vs evidence of effective intervention
- At what age?
- Pilot program overseas

NIPT impact: inevitable rise in detection

www.andrologyaustralia.org

Courses for GPs

accredited education provider via RACGP

	Course description	Type	RACGP QI& CPD Points	
Younger male health	male infertility, testicular cancer, Klinefelters, premature ejac. prostatitis	Online ALM (Free)	40 Category 1	30 PRPD points
Older male health	androgen deficiency, erectile dysfunction & co-morbid disease, prostate disease.	Online ALM (Free)	40 Category 1	30 PRPD points
Aboriginal and Torres Strait Islander males	Tailored knowledge and skills to initiate dialogue and engagement	Male Health Education DVD (Free)	4 Category 2	2 Core points
Men's sexual and reproductive health	Postgraduate Unit Dept. of General Practice, Monash Univ.	Distance education (Fee-payable)	Contact the Coordinator