# Prader Willi Syndrome and Hypogonadism

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## No Conflict of Interest to Disclose

## Objectives

- **Identify the clinical features of hypogonadism and incomplete / delayed puberty in a male with Prader Willi syndrome (PWS)**
- **Understand the role of hCG in evaluation and treatment of hypogonadism in PWS**
- **Discuss expert recommendations for the treatment of hypogonadism in males with PWS**

## Introduction

- **PWS is a multisystem genetic disorder (15q11.2-q13)**
- **Complex phenotype likely caused by hypothalamic dysfunction leading to hormonal dysfunction and the absence of satiety**
- **Hypotonia and hypogonadism are the first manifestations of a primitive hypothalammic alteration, which many believe is the basis of PWS**

## Introduction

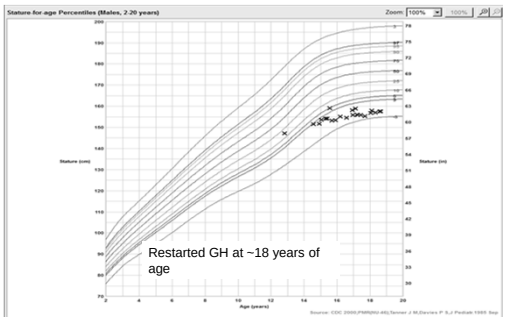
- **Hypogonadism is a common clinical feature of PWS which confirms the importance of hypogonadism as a major diagnostic criterion of PWS**
- **Patients with PWS commonly fail to spontaneously initiate or complete puberty**
- **However, many have premature adrenarche**
- **Precocious puberty is more rare**

## Case Study Hypogonadisn in PWS
### Currently 19 year old male

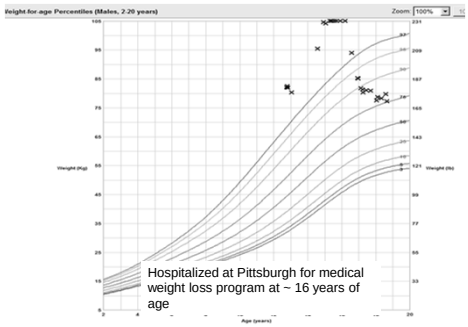
**History:**

- **Diagnosed clinically at age 2 years, and at 6 years based on methylation studies; Consistent with imprinting abnormality***
- **Hypotonia and poor feeding in the newborn period Developmental delay and hyperphagia in the early childhood years**
- **Seen at outside institution, on GH for 6 months, but therapy stopped due to hyperglycemia**
- **Lost to follow up until age 14 years, when referred by PCP regarding micropenis and crypto-orchidism**

## Case Study Hypogonadisn in PWS Stature




## Case Study Hypogonadisn in PWS Weight




## Case Study Hypogonadisn in PWS Concurrent Health Issues

- **Obesity**
- **Sleep apnea- on CPAP***
- **A lot of daytime tiredness and fell asleep easily**
- **History of strabismus (wears corrective lenses)**
- **History of behavioral problems**
- **Vitamin D insufficiency 21 ng/mL, improved to 29 ng/mL after taking 2000 units daily from April-November 2013**
- **Normal Ca, Phos, Alk Phos**
- **Diabetes T2**

## Case Study Hypogonadisn in PWS
### Initial Evaluation in Endocrine Clinic

- **Age 14 years; clinic visit after lost to follow up**
- **Acanthosis nigricans**
- **BMI: 41kg / m2**
- **Tanner 2 PH, large suprapubic fat pad, stretched penile length difficult to measure but was ~ 3.5 cm, testicles not palpable**
- **Plan to obtain gonadotropin and testosterone blood work, bone age, refer to urology and PWS clinic**

## Case Study Hypogonadisn in PWS
### Results

**Pre-pubertal Testosterone, LH, FSH**

| | 2<br>10/5/2010<br>1434 |
|---|---|
| FOLLICLE STIMULATI... | *0.045 ** |
| TESTOSTERONE, TOTAL | *15 ** |
| LH BY ICMA | *0.021 ** |
| FREE TESTOSTERONE | *1.8 ** |
| FREE TESTOSTERONE (%) | *1.2 ** |
| SEX HORMONE BINDIN... | *22 ** |

**Ranges**

- **FSH: Tanner1, 0.26 – 3**
- **T: Tanner 1, <3 - 10**
- **LH: Tanner 1, 0.02 - 0.3**
- **Free T: Adult Males: 52 - 280**
- **Free T %: Adult Males: 1.5 - 3.2**
- **SHBG: Pubertal Males: 16 - 100**

## Case Study Hypogonadisn in PWS
### Results

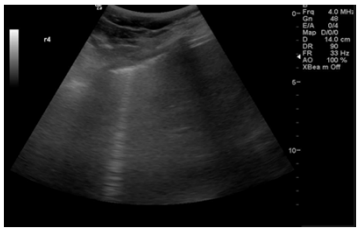
**Bone Age Reading**

- **Chronological age 14 years 1 month**
  **Bone age 16 years**
- **Previously on GH therapy at outside institution, was stopped due to hyperglycemia**

## Case Study Hypogonadisn in PWS

- **15 years**
- **Very prominent suprapubic fat pad which completely engulfed his penis; circumcised but fairly small in size**
- **Scattered thin pubic hair**
- **Testicles were difficult to feel. Possibly palpated right testicle higher up above the scrotum; could not palpate left testicle**
- **Referred to Urology**

## Case Study Hypogonadisn in PWS
### Scrotal Ultrasound



**Testes not identified**

## Case Study Hypogonadisn in PWS
### Urology Plan

**"Because this is a much older child and he is morbidly obese, I think that it may be helpful to obtain a scrotal ultrasound to locate the testicles and assess their size**

**Performing orchidopexy in this young man would be extremely difficult because of his age and size in addition to the anesthetic risks because of his obesity**

**There is no guarantee that the testicles would function properly, even after surgery**

**Discuss the situation with endocrinology"**

## Case Study Hypogonadisn in PWS

- **Plan to do hCG stimulation testing, monitor for rise in testosterone indicating presence of testes, then repeat scrotal ultrasound with anticipated enlargement of testes***
- **Administer hCG, 1500 units/m2 (3000 units) twice per week**
- **Draw total testosterone 3 days after every other hCG injection**
- **For example, hCG Monday, hCG on Friday, then hCG injection and testosterone level on Monday**
- **Continue for up to 6 weeks. Stop test if testosterone level reaches 300 ng / dl**

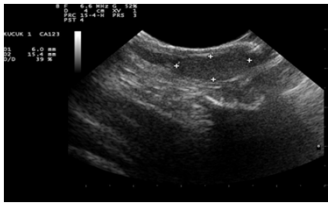
## Case Study Hypogonadisn in PWS
### Results

**hCG Stimulation Test Results**

**Rise in testosterone, but overall below reference range 100-500 ng / dL**

| | 5<br>9/18/2012<br>0823 | 4<br>9/24/2012<br>1610 | 3<br>10/1/2012<br>1603 | 2<br>10/8/2012<br>1608 |
|---|---|---|---|---|
| MET / ENDO | | | | |
| TESTOSTERONE | *24 **  | *59 **  | *90 **  | *92 **  |

## Case Study Hypogonadisn in PWS
### Repeat Scrotal Ultrasound



**Testes identified**

## Case Study Hypogonadisn in PWS

**Scrotal Ultrasound Report**

- **On US he had small, ovoid hypoechoic structures in inguinal canals bilaterally**
- **No vascularity on doppler**
- **Essentially, testes were present, but small and atropic**

## Case Study Hypogonadisn in PWS
### Case Management

**Laparotomy**

- **Diagnostic laparotomy performed February 2013 with potential for orchidopexy, age 17 years**
- **Orchiectomy was performed**
- **Pathology report showed infantile, atrophic changes with no evidence of spermatogenesis**

## Case Study Hypogonadisn in PWS
### Case Management

**Testosterone Dosing IM (Q month)**

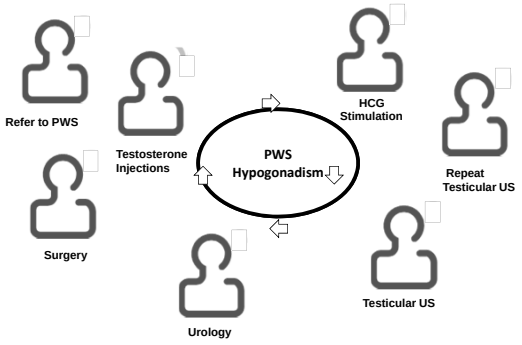
- **Testosterone 50 mg started in April 2013**
- **Increased to 100 mg in Novemeber 2013**
- **Increased to 150 mg in June 2014**
- **Increased to 200 mg in February 2015**

## Case Study Hypogonadisn in PWS
### Case Management

**Response to Testosterone**

- **At testosterone dose of 100 mg monthly:**
  - **Penis increased to 6 cm x 2 cm**
  - **Tanner stage 4 pubic hair**
  - **Axillary hair present**
- **At testosterone dose of 150 mg monthly:**
  - **Noted voice change**
  - **Noted increased assertiveness**
  - **No noted aggression or anger**

## Case Study Conclusion

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## Hypogonadism in Males with PWS

- **Cryptorchidism in~ 80-100%**
- **Small testes ~76%**
- **Scrotal hypoplasia 69%**
- **Incomplete, delayed, or disordered pubertal development**
- **Premature adrenarche common ~14%**
- **Premature puberty can occur ~3%**
- **No reports of paternity from PWS men**
- **Testosterone levels often subnormal but lower SHBG can raise free testosterone**

(Goldstone AP *et al,* 2008)

## Hypogonadism in Males with PWS

**Prevalence of genital abnormalities and pubertal findings in PWS subjects**

Table 2 Prevalence of genital abnormalities and pubertal findings in PWS subjects

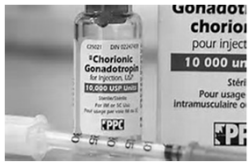
| | | | | | |
|---|---|---|---|---|---|
| Males | Cryptorchidism | Small testes | Scrotal hypoplasia | Micropenis | Phimosis |
| $n = 42$ (14.2 ± 9.3 years) | 42/42 (100%) | 32/42 (76%) | 29/42 (69%) | 15/42 (36%) | 13/42 (31%) |
| Females | Hypoplasia of clitoris and/or labia minora | Primary amenorrhea (aged > 15 years) | Menarche ($n = 32$ > 15 years) | Secondary amenorrhea | |
| $n = 42$(17.5 ± 6.7 years) | 32/42 (76%) | 18/32 (56%) | 14/32 (44%) | 6/14 (43%) | |

(Crino *et al*, 2003)

## Hypogonadism in Males with PWS

**What about hCG?**

TREAT




NOT TO TREAT


## Role of Hcg in Treatment of Males with PWS

**Diagnostic Management of Cryptorchidism**

**American Urological Association : Guideline Statement 3**

- **Refer infants with a history of cryptorchidism (detected at birth) who do not have spontaneous testicular descent by six months ***
- **Testes that remain undescended by six months are unlikely to descend spontaneously**
- **The rationale for referral for orchidopexy by six months is the low probability of spontaneous descent and the probable continued damage to testes that remain in a non-scrotal location.**

(American Urological Association, 2014)

## Role of hCG in Treatment of Males with PWS

**Treatment Management of Cryptorchidism**

**American Urological Association : Guideline Statement 10**

- **Providers should not use hormonal therapy to induce testicular descent as evidence shows low response rates and lack of evidence for long-term efficacy**
- **Studies show a significant risk of recurrence. An individual study may show a reasonable effect in inducing testicular descent, the overall review of all available studies fails to document long-term efficacy** (American Urological Association, 2014)

## Role of hCG in Treatment of Males with PWS

**Dr Jennifer Miller, " Approach to the child with Prader- Willi syndrome"**

**• Treatment with hCG is recommended for infant males with undescended testes because it may help with testicular descent, "more than in typical males with cryptochidism"**

**• And it improves the size of the scrotal sac if orchiopexy is needed**

(Crino *et al*, 2003;Goldstone *et al,* 2008; Miller, 2012)

## Hypogonadism in Males with PWS

**hCG may be beneficial to assess function of the testes, but may not be beneficial for treatment of undescended testes**

## Experts on Hypogonadism in PWS

- **Cryptorchidism: Address during the first or the second year, particularly because there is evidence of both primary and central hypogonadism**
- **Rare cases of testicular cancer have been reported in PWS***
- **Scrotal hypoplasia and obesity can make surgery difficult if delayed until a later age and could require repeated surgical interventions**

(Cassidy, *et al*, 2011; Goldstone, *et al*, 2008)

## Experts on Hypogonadism in PWS

- **Rare cases of testicular cancer have been reported in PWS**


(Pediatric Research, 1999)

## Hypogonadism in Males with PWS

- **Children with PWS display a specific form of combined**
- **Hypothalamic (low LH) and peripheral (low inhibin B and high FSH)**
- **Hypogonadism, suggesting a primary defect in Sertoli and / or germ cell**
- **Maturation or an early germ cell loss. hCG therapy stimulates testosterone production and virilization**

(J Clinical Endocrinology Metabolism, 2006)

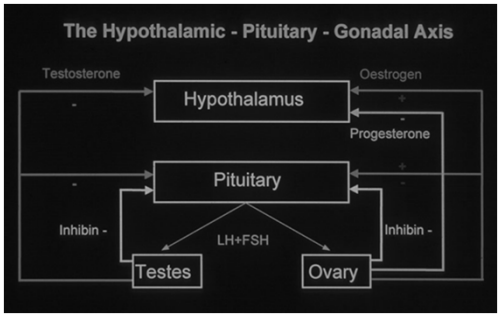
## Hypogonadism in Males with PWS

**Testicular Failure After Puberty Onset**

- **Boys have normal inhibin B levels until age 10 yrs, but after puberty onset inhibin B levels declined to < 5% tile and FSH increased to > 95 % tile**
- **Testosterone increased with puberty but remained < 5% tile**
- **LH increased but not above 95 % tile**
- **Major cause is primary hypogonadism**

(Siemensma EP et al, 2012)

## Normal Puberty



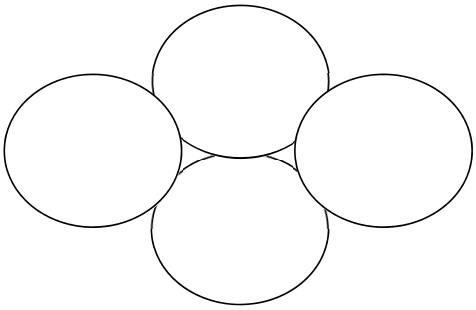

(Myer, date unknown)

## Effects of Hypogonadism in PWS Males

- **Likely contributes to decrease in bone and muscle mass and increase in body fat**
- **Severe obesity in PWS contributes to mortality and decreased quality of life**

## What about Testosterone Replacement?


## What about Testosterone Replacement?



## Japanese Study with PWS Males

**Japanese study of 22 PWS male patients age 16 and 48 years; serum Testosterone < 300**

**Patients with existing modified overt aggression scale > 4 excluded**

***Example:***

- **Threatens violence toward self or other; repeatedly or deliberately**
- **Sets fires; throws objects dangerously**
- **Inflicts major injury on self or makes a suicide attempt**
- **Attacks others, causing serious injury (fracture, loss of teeth, deep cuts, loss of consciousness, etc)**

(Kido et al, 2013)

## Japanese Study with PWS Males

- **Measurements prior to testosterone replacement and 1 month after last injection**
- **Testosterone 125 mg IM monthly**
- **Measurements: pubertal stage, body hair, T, LH, FSH, HGB/HCT, HDL, AST/ALT, Chol, Trigs, LDL, BG, A1C**
- **Measured erectile dysfunction, ejaculation, spermatogenesis**
- **Measured DEXA, BMI, % body fat**
- **MOAS- aggression scale**

(Kido *et al,* 2013)

## Japanese Study with PWS Males After Two Years

- **Increased pubic hair 16/22 patients**
- **Emergence of erectile function 8/22 patients**
- **Ejaculation 3/22 patients**
  - **No sperm in samples**
- **1 month post-injection Testosterone levels all <300**
- **Improvement in DEXA and body composition**
- **No change in aggression**
- **Non-significant increase in HGB/HCT**
- **Non-significant decrease in HDL**

(Kido *et al,* 2013)

## Treatment for Hypogonadism in PWS

**Recommendations: Expert care meeting on PWS 2008**

- **No standardized protocols for sex hormone treatment nor prevention of osteoporosis**
- **Benefits of treatment include prevention of osteoporosis and fracture**

## Expert Treatment of Hypogonadism in PWS

**Hormone replacement:**

- **Low dose testosterone (injections, transdermal patch or gel) using escalating doses every 3- 6 months to allow testosterone to get to normal level or HCG injections**

(Cassidy, *et al*, 2011;Goldstone, *et al*, 2008)

## Expert Treatment of Hypogonadism in PWS

- **Monitor androgen status annually during adolescence and adulthood**
- **DEXA as clinically indicated**
- **Consider gonadal hormone replacement**

(Cassidy, *et al*, 2011;Goldstone, *et al*, 2008)

## Body Image and Sexual Interests in PWS

**PWS FYI:**

- **Half of patients reported having been on a date and kissing romantically**
- **All males and 64% females wished to marry**
- **77% of males wanted hormonal treatment to increase phallic size**
- **43% of females wanted hormonal treatment to achieve regular menstruation**
- **No correlation between hormonal levels and sexual interests**

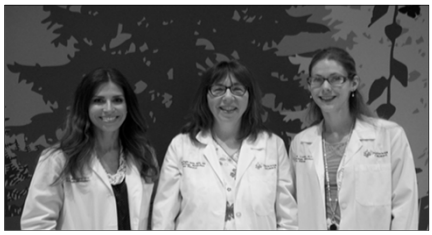
(Gross-Tsur *et al*, 2011)

## Questions

Thomas A. Edison

**"We don't know a millionth of one percent about anything."**

## A Special Thanks



**Dr Kathryn Obrynba**
**Lead PWS Endocrinologist**

**Dr Loyal Coshway**
**Endocrine Fellow**

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