5th Asia Pacific Prader-Willi Syndrome Conference

Endocrinology Care in Prader-Willi Syndrome

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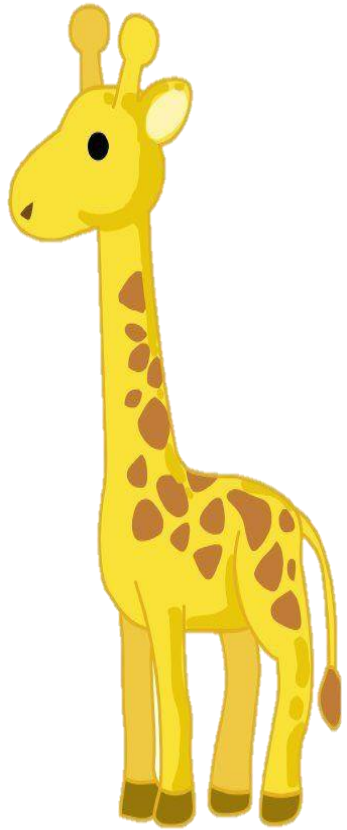
Plan of Talk

- **Prader-Willi Syndrome**
- Growth disorder
  - GH treatment in children
    - Indication/Aims
    - When to start?
    - Benefits
    - Contraindications & Warnings
    - Management Plan & Monitoring
  - Adult PWS
- Hypogonadism
- Hypothyroidism
- Hypoadrenalism



Prader-Willi Syndrome

- Lack of expression of genes on the paternally derived chromosome 15q11-q13.
  - paternal alleles are defective, missing or silenced; 75% paternal deletion 15q11-q13
  - 24% maternal uniparental disomy
  - 1% imprinting error

Nicholls RD et al Nature 1989 342:281-285
Driscoll DJ et al Genomics 1992 13:917-924

- Characteristic phenotypes:
  - Severe neonatal hypotonia
  - Early onset hyperphagia
  - Development of:
    - short stature
    - learning disability
    - behavioural problem

Holm VA et al Pediatrics 1993 91:398-402
Gunay-Aygun M Pediatrics 2001 108:E92

Metabolic and Endocrine Dysfunction

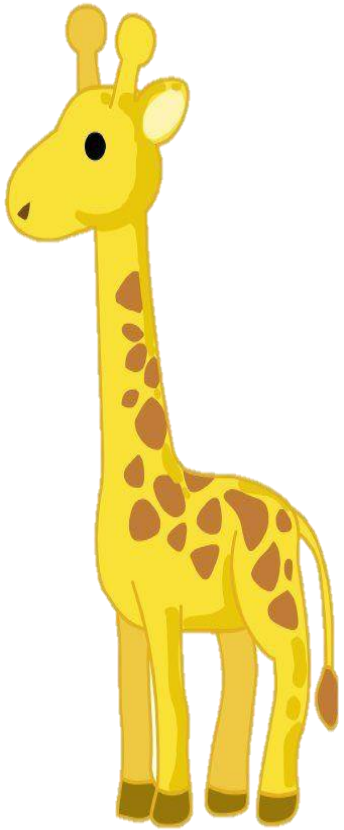
- Hypothalamic-pituitary dysfunction leads to **metabolic problems**:
  - No satiety → insatiable appetite → obesity (morbid, progressive obesity)
  - Glucose intolerance
  - Cardiovascular disease; hypertension, hyperlipidaemia

- Hypothalamic-pituitary dysfunction leads to **endocrine abnormalities**:
  - Growth dysfunction
  - Hypogonadism
  - Hypothyroidism
  - Hypocortisolism

P BURMAN, E. MARTIN RITZE´N, AND A C LINDGREN. Endocrine Dysfunction in Prader-Willi Syndrome: A Review with Special Reference to GH
Muscogiuri G et al Reviews in Endocrine and Metabolic Disorders (2019) 20:239–250

Plan of Talk

- Prader-Willi Syndrome
- **Growth disorder**
  - **GH treatment in children**
    - **Indication/Aims**
    - **When to start?**
    - **Benefits**
    - **Contraindications & Warnings**
    - **Management Plan & Monitoring**
  - **Adult PWS**
- Hypogonadism
- Hypothyroidism
- Hypoadrenalism



Growth and GH status

- Early signs
  - Mild prenatal growth retardation
    - Median BW -1.37 SDS (20% BW < -2 SDS)
    - Median birth length -0.46 SDS
  - Short stature after birth up to 2 years

- Low IGF-1 in majority (~100%) of them
- GH peak during stim test: <10 mcg/liter in 40-70%

Tauber M Growth hormone therapy in Pediatrics-20 years of KIGS 2007; 377-387
Corrias A et al J Endocrinol Invest 2000, 23:84-89
Eiholzer U et al J Pediatr 1998, 157:890-893
Burman P et al Endocr Rv 2001, 22:787-799

Growth and GH status

- At median age 6.4 years
  - median height SDS -2.2 SDS (-4.1 to -0.3)

- Mean spontaneous adult height
  - 162 cm in boys
  - 150 cm in girls.

Fridman C et al J Pediatr 2000, 76:246-250
Hauffa BP et al Acta Paediatr 2000 89:1302-1311

Growth Dysfunction

- Impaired growth: a combination of
  - growth hormone (GH)/insulin-like growth factor 1 (IGF-1) deficiency
  - lack of pubertal growth spurt

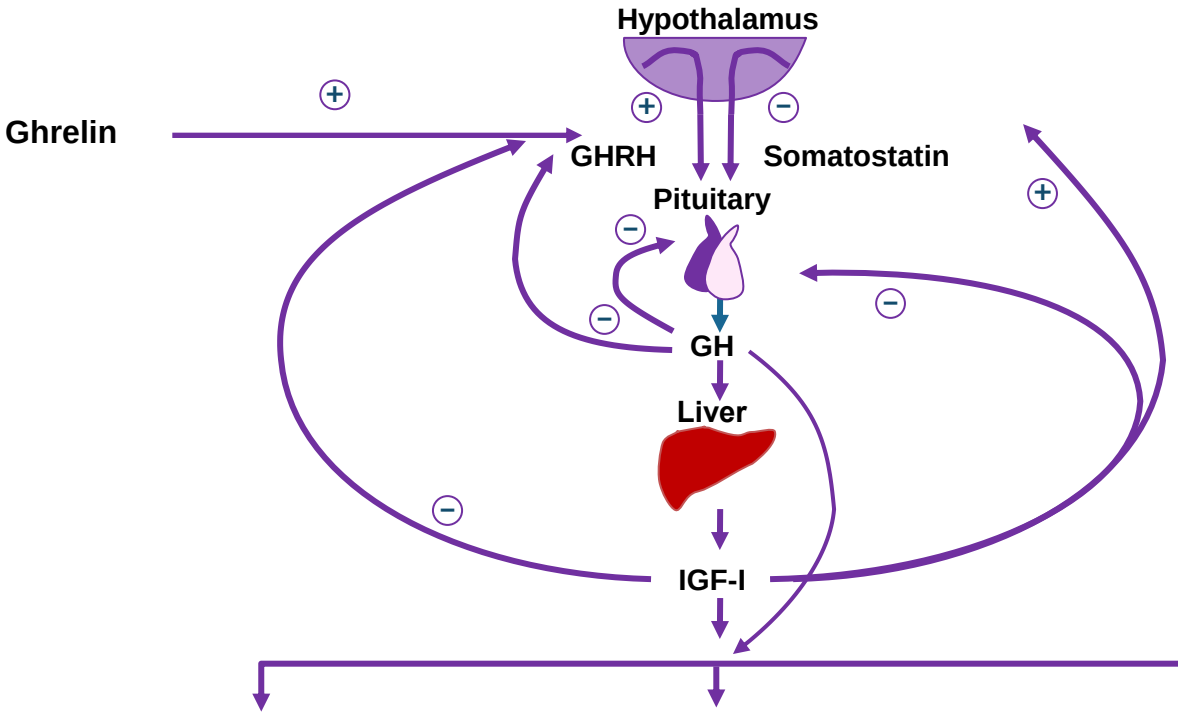
	Male Mean adult height (cm)	Female Mean adult height in (cm)	
Butler & Meaney	155	148	USA (1991)
Wollman et al	162	150	Germany (1998)
Hauffa et al	159	149	Germany (2000)
Nagai et al	148	141	Japan

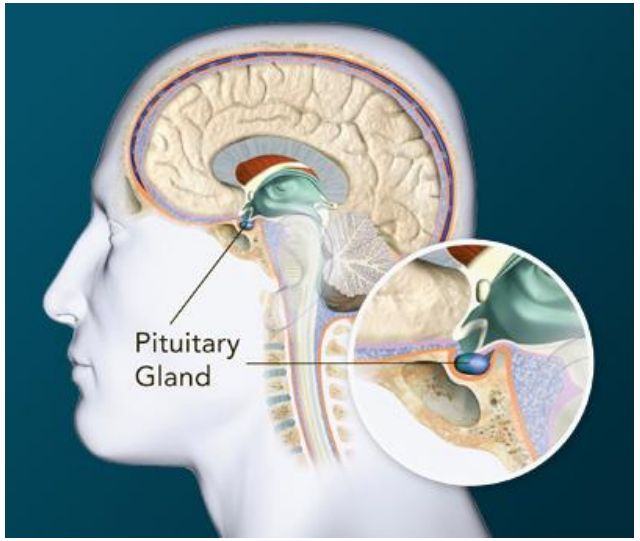
Indications for rhGH

FDA approved uses of GH (J Pediatr 143, 2003)

- Before 1995
  - GHD
  - CRF
  - Turner syndrome
- Now
  - ISS
  - SGA
  - Prader-Willi syndrome
    - USA 2000
    - Europe 2001
    - Aust 2004
  - Adults with GHD and AIDS (wasting)

Normal GH Physiology





Muscle[1,2]

- ⇧ Amino acid transport
- ⇧ Nitrogen retention
- ⇧ Lean tissue and energy expenditure

Adipose tissue[1,2]

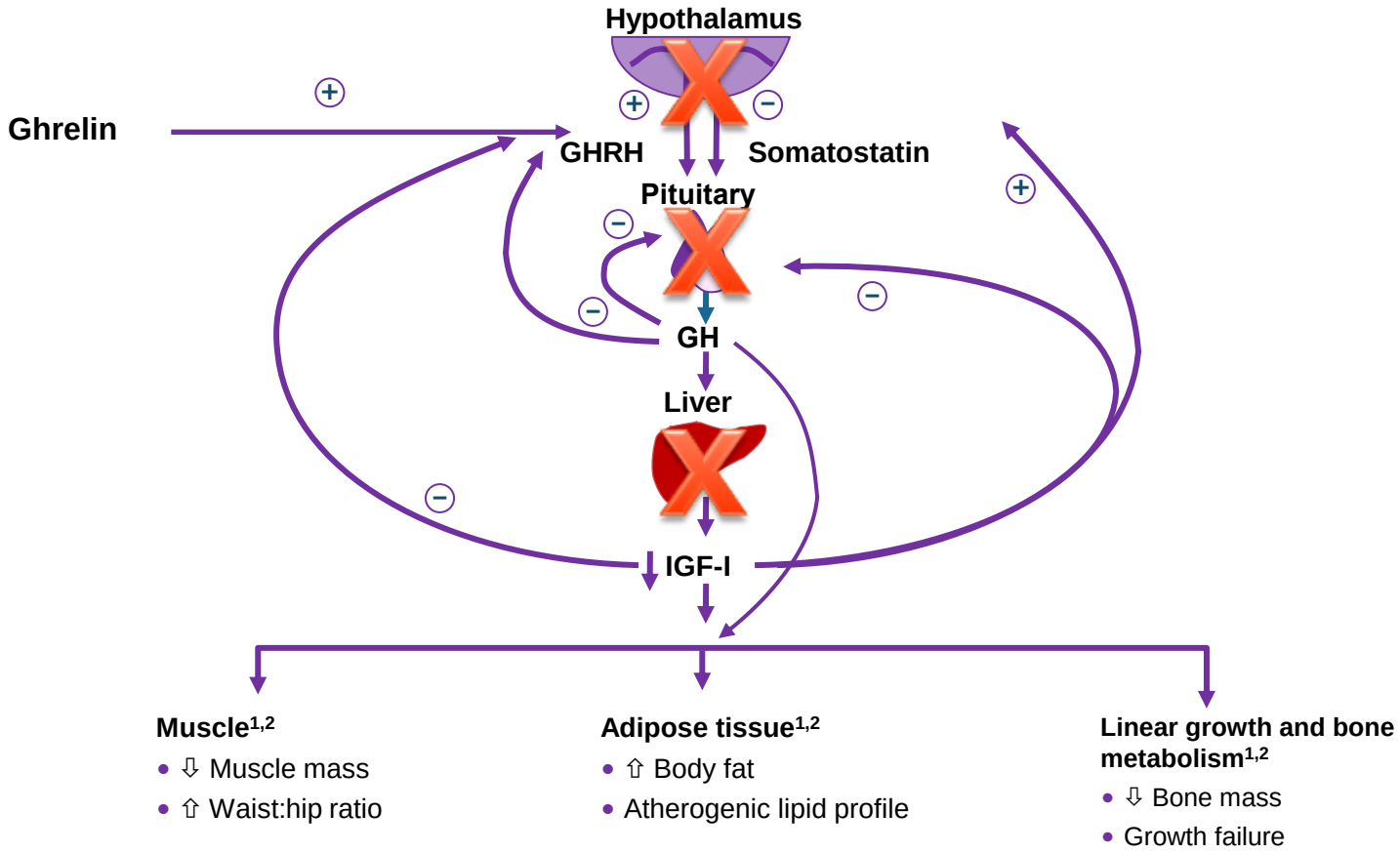
- Acute insulin-like effects
- ⇧ Lipolysis
- Inhibits lipoprotein lipase
- ⇩ Glucose transport
- ⇩ Lipogenesis

Linear growth and bone metabolism[1,2]

- Promotes epiphyseal growth
- ⇧ Bone mass

1. Rosenfeld, Cohen. In: Sperling, ed. Pediatric Endocrinology. 2nd edn, Philadelphia, PA: Saunders; 2002:211–88;
2. Gharib et al. Endocr Pract 2003;9:64–76.

Pathophysiology of GH Disorders



1. Rosenfeld, Cohen. In: Sperling, ed. Pediatric Endocrinology. 2nd edn, Philadelphia, PA: Saunders; 2002:211–88;
2. Gharib et al. Endocr Pract 2003;9:64–76.

GH therapy in PWS: Managing Teams

- **Multi-disciplinary Team (Paediatrics)**
  - Paeds Endocrinologists (Coordinator)
  - Geneticists
  - ENT specialist: upper airway obstruction (tonsils, adenoids)
  - Respiratory: Sleep study (OSA)
  - Spine specialists: Scoliosis
  - Nutritionists
  - Rehabilitation specialists: muscle strength and scoliosis management

Goldstone AP et al JCEM 2008 93(11):4183-4197
Deal et al JCEM 2013: 98(6), E1072-1087

GH therapy in PWS

- **Indications**:
  - Poor height gain
  - Poor muscle strength or delayed motor development

- **Aims**: to improve
  - psychomotor development
  - growth during childhood & attain normal adult height
  - body composition

Burman P et al Endocr Rev 2001, 22:787-799
Deal et al JCEM 2013: 98(6), E1072-1087

GH therapy in PWS

- **Exclusion criteria**:
  - severe obesity
  - uncontrolled diabetes
  - untreated severe obstructive sleep apnea
  - active cancer
  - active psychosis

  - Scoliosis and cognitive impairment **should NOT** be considered a contraindication

Burman P et al Endocr Rev 2001, 22:787-799
Deal et al JCEM 2013: 98(6), E1072-1087

GH therapy in PWS

- **Challenges**:
  - treating individuals with cognitive disability
  - varied therapeutic goals that are not focused exclusively on increased height
  - potential life-threatening adverse events

Burman P et al Endocr Rev 2001, 22:787-799
Deal et al JCEM 2013: 98(6), E1072-1087

When to start rhGH?

- No consensus on age of rhGH start
- Treat before the onset of obesity, ie by 2 years of age.

- Current evidence: as young as **4-6 months old**; to improve
  - motor development
  - muscular tone
  - cognition

Carrel AL et al J Pediatr 2004, 145:744-749
Dykens et al J Child Psychol Psychiatri 2017
Deal et al JCEM 2013: 98(6), E1072-1087
Festen DAM et al Clinical Endocrinol 2008, 68:919-925

GH therapy in PWS: Dosing

- Previously:
  - start at 9-12 mcg/kg/day
  - standard dose 25-35 mcg/kg/day

- Current recommendation:
  - start 0.5 mg/m2/day
  - standard dose 1.0 mg/m2/day

- Adjust dose based on growth response or IGF-1 levels

Tauber M Horm Res 2000
Goldstone AP et al JCEM 2008 93(11):4183-4197
Deal et al JCEM 2013: 98(6), E1072-1087

GH therapy in PWS: Benefits

- **Significant pre-pubertal height gain:**
  - KIGS data (N= 522; 54.8% boys)
    - Start: mean height **-2.05** (1.46) SDS
    - After 3 years: height: **-0.31** (1.34)

- **Significant height gain: Final adult height**
  - KIGS data (N= 173; 46.8% boys)
    - Start: mean height **-2.14** (1.40) SDS
    - Final adult height/near adult height: **-1.19** (1.37) SDS
    - mean (SD) Ht - MPH SDS was **-1.05** (1.21)

Bakker et al JCEM 2017;102(5): 1702-1711

GH therapy in PWS: Benefits

	Male Mean adult height (cm)	Female Mean adult height (cm)	
Butler & Meaney	155	148	USA (1991)
Wollman et al	162	150	Germany (1998)
Hauffa et al	159	149	Germany (2000)
Nagai et al	148	141	Japan
Bakker et al (treated with rhGH)	**170.1**	**155.8**	**KIGS Database (2017)**

Bakker et al JCEM 2017;102(5): 1702-1711

GH therapy in PWS: Benefits

Table 3. Growth Data and BMI Until Adult Height in 173 Adolescents With PWS

Characteristic	Baseline	One Year	Start Puberty	Adult Height
Age, y	8.2 (2.7)	9.1 (2.5)	12.1 (2.3)	17.4 (1.7)
Years of GH			3.7 (2.4)	8.7 (2.7)
Bone age delay[a]	1.2 (1.5)		0.3 (1.5)	
Height SDS	−2.1 (1.4)	−1.2 (1.3)	−0.2 (1.3)	−1.2 (1.4)
Height SDS PWS	−0.5 (1.0)	0.1 (1.1)	0.8 (1.4)	1.6 (1.5)
Ht-MPH SDS	−2.1 (1.4)	−1.1 (1.3)	−0.1 (1.2)	−1.1 (1.2)
HV, cm/y	5.2 (2.3)	9.8 (2.4)		
HV SDS	−1.1 (2.5)	5.5 (3.4)		
Pubertal delta height,[b] cm				17.4 (10.5)
Weight SDS	0.4 (1.7)	0.5 (1.5)	0.8 (1.6)	1.2 (1.6)
BMI SDS	1.9 (1.3)	1.4 (1.3)	1.4 (1.2)	1.8 (1.3)
BMI SDS PWS	−0.2 (1.0)	−0.6 (1.0)	−0.7 (1.0)	−0.6 (1.1)

Bakker et al JCEM 2017;102(5): 1702-1711

GH therapy in PWS: Benefits

- **Body composition, motor function, fat mass**
  - Decrease in % body fat in 1st year and stabilization in 2nd year and onwards
  - Increase lean body mass during first 2 years
  - Improve physical strength and agility
  - Decrease subcutaneous fat volume
  - Lower visceral fat and thigh fat
  - Increase HDL and reduced LDL

Carrel AL et al, JCEM 2010, 95: 1131-1136
Tanaka Y et al Am J Med Genet A 2013; 161:27-33

GH therapy in PWS: Benefits

- **Better cognitive performance**
  - N=127, age 4-21 years (USA)
    - Improve cognitive performance
    - Higher Verbal and Composite IQ scores
    - Better communication
    - Better daily living skills
    - “earlier is better”, starting before 12 months had higher non-verbal and composite IQ score compared to those started by age 1-5 years

Festen DA et al Clin Endocrinol 2008; 68: 919-925
Siemensma EP et al JCEM 2012; 97:2307-2314
Dykens et al J Child Psychol Psychiatri 2017

GH therapy in PWS: Benefits

- **Bone mineral density (Dutch PWS Cohort)**
  - N=77 (37 boys) pre-pubertal children on GH for 4 years and 64 (33 boys) pubertal children on GH for 9 years
  - Dose 1 mg/m2/day (0.035 mg/kg/day)
  - BMD total body and lumbar spine
  - Results:
    - **Pre-pubertal BMD increased significantly**
    - Pubertal: BMD decreased significantly, but within normal; significantly associated with Tanner staging (pubertal development)
  - Conclusion: clinicians should **start sex hormone therapy** from the age of **11 years in girls** and **14 years in boys** unless there is a normal progression of puberty

Bakker et al JCEM 2015;100: 1609-1618

GH therapy in PWS: BMD

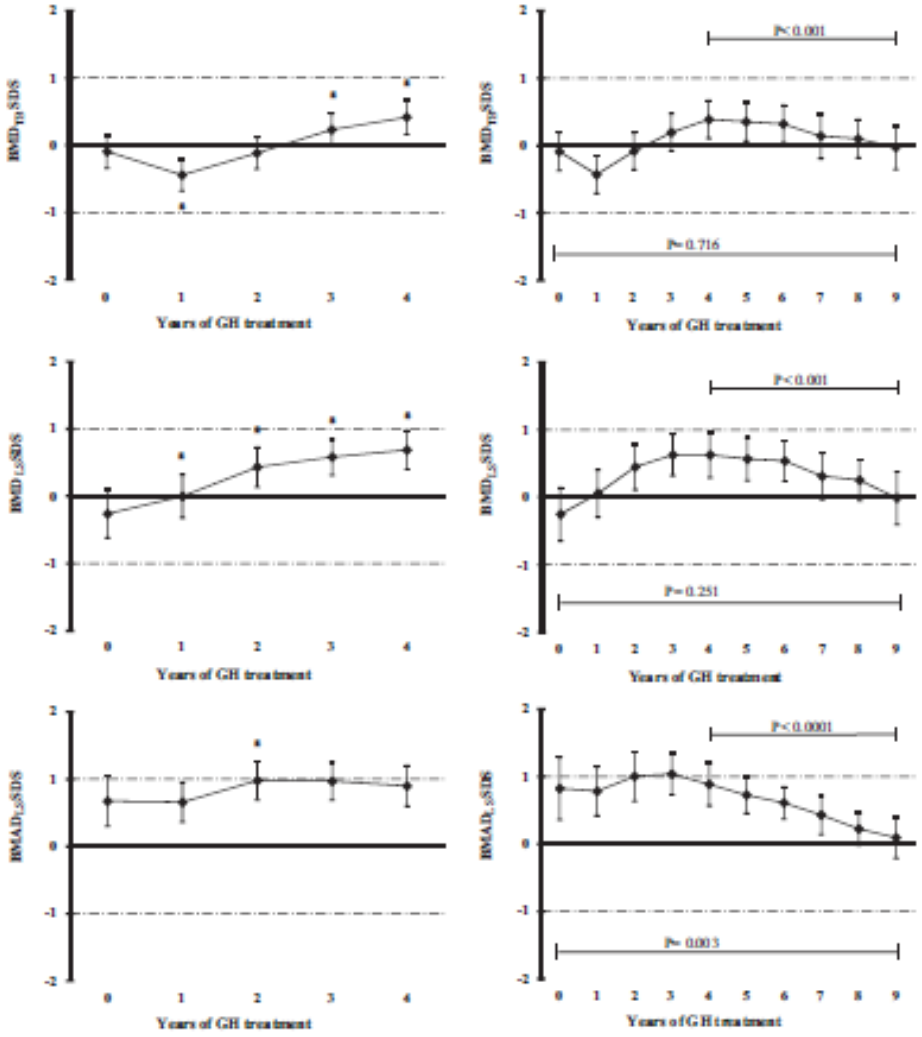


Figure 1. BMD_{TB}, BMD_{LS}, and $BMAD_{LS}$ SDS in prepubertal children with PWS during 4 years of GH treatment. *, $P < .05$, compared with baseline.

Figure 2. BMD_{TB}, BMD_{LS}, and $BMAD_{LS}$ SDS during 9 years of GH treatment.

Bakker et al JCEM 2015;100: 1609-1618

GH therapy in PWS: other OUTCOMES

- Safety study up to 8 yrs

Bakker NE et al. Eight years of growth hormone treatment in children with PWS: maintaining the positive effects. J Clin Endocrinol Metab. 2013;98:4013–4022.

- Recent reviews: GH use in PWS remains supportive

Bridges N. What is the value of GH therapy in PWS? Arch Dis Child, October 2003

Grugni G et al Therapeutics and Clinical Risk Management 2016: 12:873-881

- No change in **scoliosis progression** in children with PWS treated with GH

Nagai T et al. GH therapy and scoliosis in patients with PWS. AJMG 2006

Murakami N et al. Scoliosis in PWS, effect of GH therapy Am J Med Genet A 2012

- **CVS risk improve** after GH treatment

l'Allemand D, Eiholzer U, Schlumpf M, Steinert H, Riesen W. Cardiovascular risk factors improve during 3 years of GH therapy in PWS. Eur J Pediatr 2000;159:835-42.

GH therapy in PWS

- **Warnings**
  - Sleep apnoea
    - High risk of death during first 9 months
  - Upper airway obstruction
    - adenoid and/or tonsil hypertrophy
  - Severe respiratory impairment
  - Changes in glucose tolerance
    - impaired OGTT prior to treatment
    - obese
    - strong family history of diabetes

Tauber M et al Am J Med Genet A 2008, 46:881-887
Deal et al JCEM 2013: 98(6), E1072-1087

GH treatment in PWS: ADVERSE OUTCOME

- Death in PWS after GH: mostly related to respiratory disordered breathing and associated infection
- Ongoing debate on use or not to use GH in children with PWS (OSAS vs insufficiency of respiratory muscle and pharyngeal narrowness)

Tauber M, Diene G, Molinas C, Hébert M. Review of 64 cases of death in children with Prader-Willi syndrome (PWS) Am J Med Genet A. 2008;146:881–887.

Eiholzer U, Nordmann Y, L'Allemand D. Fatal outcome of sleep apnoea in PWS during the initial phase of growth hormone treatment

Bakker B, Maneatis T, Lippe B. Sudden death in Prader-Willi syndrome: brief review of five additional cases. Concerning the article by U. Eiholzer et al.: Deaths in children with Prader-Willi syndrome. A contribution to the debate about the safety of growth hormone treatment in children with PWS (Horm Res 2005;63:33-39) Horm Res. 2007;67:203–204.eatment. A case report. Horm Res. 2002;58(Suppl 3):24–26.

GH therapy in PWS: Management

- **Before starting GH**
  - Genetic confirmation
  - Nutritional evaluation, and body composition
  - Control of food, esp if obese
  - Complete clinical evaluation of sleep and breathing
    - ENT assessment and polysomnography are mandatory if there is snoring, enlarged tonsils etc

Goldstone AP et al JCEM 2008 93(11):4183-4197
Deal et al JCEM 2013: 98(6), E1072-1087

GH therapy in PWS: Management

- **Before starting GH**
  - Evaluate IGF-1
  - GH stimulation testing is not required as part of the therapeutic decision-making process
  - Oral glucose tolerance test
    - obese or >12 years old with f/hx of DM
  - Scoliosis evaluation, x-ray
  - Evaluation of hypothyroidism & hypoadrenalism

Goldstone AP et al JCEM 2008 93(11):4183-4197
Deal et al JCEM 2013: 98(6), E1072-1087

GH therapy in PWS: Management

- **While on GH treatment**
  - 3-6 monthly clinical assessment:
    - height, weight, BMI, body composition
    - scoliosis
    - adverse events
  - 6-12 monthly IGF-1: avoid high IGF-1 (> +2 SDS)
  - Fasting glucose, HbA1c, OGTT
    - if previously IGT, obese or strong f/hx of DM, >12 years
  - Yearly thyroid function (hypothyroidism)
  - Lipid profile, liver function/US (NAFLD)

Goldstone AP et al JCEM 2008 93(11):4183-4197
Deal et al JCEM 2013: 98(6), E1072-1087

GH therapy in PWS: Management

- **While on GH treatment**
  - ENT assessment and polysomnography: first 6 months
  - Worsening sleep-disordered breathing, snoring, enlarged tonsils/adenoids:
    - Mandatory ENT assessment and polysomnography
  - X-ray ± orthopaedic assessment for scoliosis
  - Yearly bone age
  - Clinical assessment of body composition every 6–12 mo by 1 or more of the following:
    - waist circumference
    - skinfold thickness
    - dual-energy x-ray absorptiometry

Goldstone AP et al JCEM 2008 93(11):4183-4197
Deal et al JCEM 2013: 98(6), E1072-1087

Monitoring Schedule

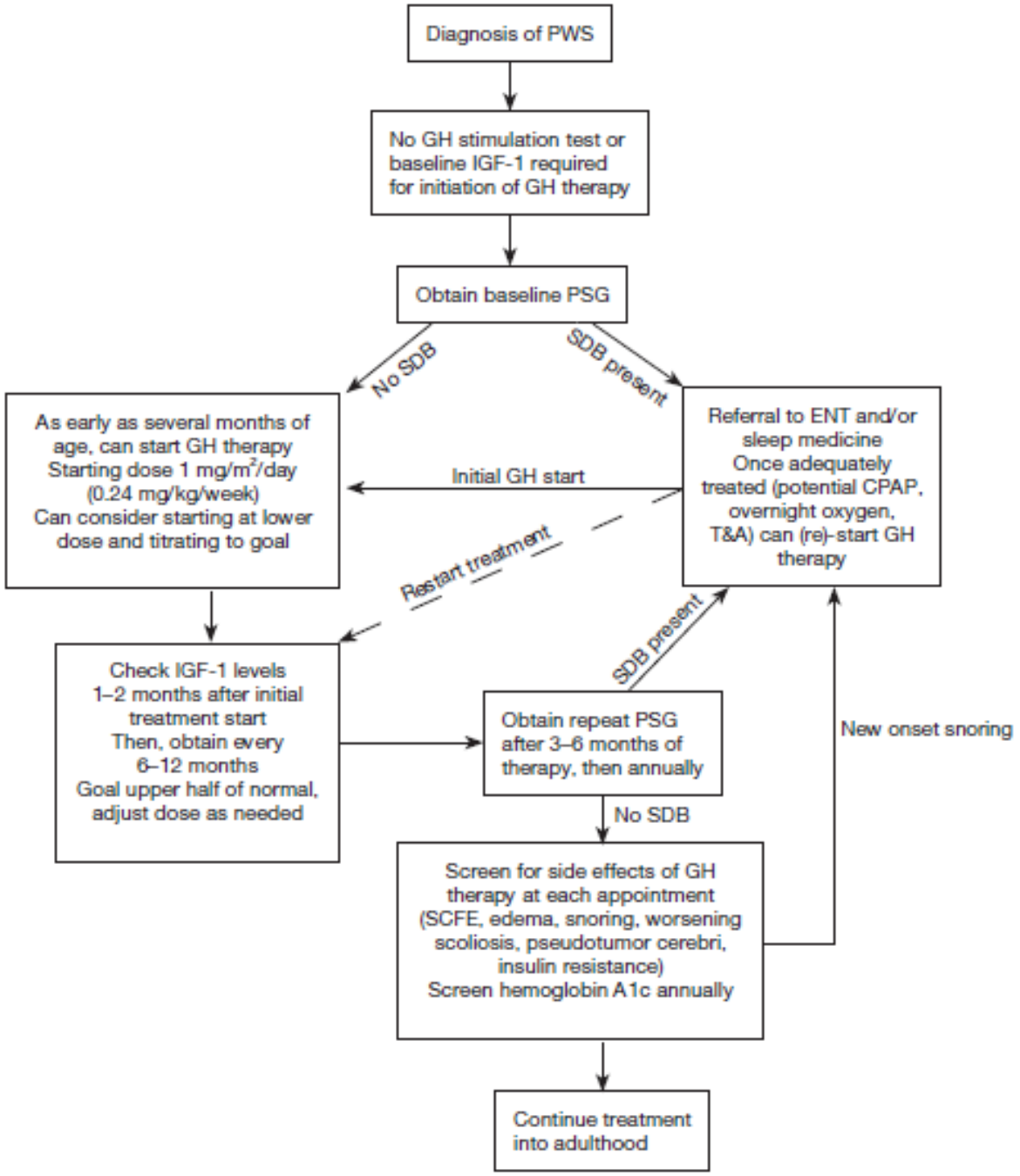
Visit assessment	Screen	Start	3 mths	6 mths	9 mths	12 mths
GH provocation test	X					
Medical, family and growth history	X					
Auxology	X	X	X	X	X	X
Bone age determination	X					X
IGF-1		X		X		X
FBS, HbA1c and insulin, OGTT		X				X
ENT assessment/polysomnography	X			X		X
Adverse event recording Sleep apnoea/snoring Scoliosis Hypothyroidism (yearly TFT)	X	X	X	X	X	X

GH therapy in PWS: Management

- **Cessation of GH**
  - Uncontrolled progression of obesity
  - Worsening glycaemic control despite
    - weight control, diabetic medication, and normal IGF-1
  - Worsening sleep-disordered breathing despite
    - weight control
    - tonsillectomy, adenoidectomy
    - normal IGF-1
  - Attainment of adult height (if for height)

Goldstone AP et al JCEM 2008 93(11):4183-4197
Deal et al JCEM 2013: 98(6), E1072-1087

Algorithm for GH treatment in PWS



GH use in PWS

ZA

- Boy, DOB 27/8/2010
- BW 3042 grams, length 47 cm, OFC 35.5 cm
- Neonatal hypoglycaemia
- Hypotonia
- Right undescended testes

- Diagnosed PWS at age 6 months
  - Absence of paternal allele 15q11-q13, FISH showed no deletion
  - Likely UPD/imprinting error

ZA

- Referred for rhGH at age 11 months
  - Weight 7.05 kg
  - Length 66.9 cm
  - No head control, floppy, dev age 5 months
- Started rhGH at 12 months

10 years later

TKL

- Girl, DOB 26/8/2010
- BW 2240 grams (private hosp)
- Hypotonia and poor feeding
- Ventilated for pneumonia at 2 months old

- Diagnosed PWS at age 2 months
  - paternal deletion 15q11-q13

TKL

- Referred for rhGH at age 16 months
  - Weight 6.45kg
  - Length 72.6cm
  - Poor head control, floppy
  - Mild scoliosis
  - No OSAS, overnight SpO2 monitoring: no desaturation

- Started rhGH at 19 months old at 12 mcg/kg/day
- increasing slowly to 25 mcg/kg/day
- Head control, sitting after 2 months


LAGU SEKOLAH
Sekolah Sri Bestari
Seindah nama dan erti
Berdiri megah tersergam indah
Berani bina sejarah
Kami anak Bestari
Mengukir nama dan pekerti
Menimba ilmu membina diri
Mengamal budaya murni
Majulah Bestari maju
Teruskan sampai ke mercu
Gemilang terus gemilang
Bestari pasti cemerlang
Kami pelapis Negara
Bersatu bersemangat waja
Maju dan mara bersama
Bestari pasti berjaya
RUKUN NEGARA
Maka kami, rakyat Malaysia berikrar akan menumpukan seluruh tenaga dan usaha kami untuk mencapai cita-cita tersebut berdasarkan prinsip-prinsip berikut :
• Kepercayaan kepada Tuhan
• Kesetiaan kepada Raja dan Negara
• Keluhuran perlembagaan
BESTARI

GH therapy in PWS Adults

- **Indications**:
  - PWS adults with growth hormone deficiency

- **Aims**: improve
  - body composition
  - lipid metabolism
  - physical and psychosocial functioning
  - cognitive function and QoL

Burman P et al Endocr Rev 2001, 22:787-799
Van Nieuwpoort IC et al Horm Behav 2011; 59:444-450
Deal et al JCEM 2013: 98(6), E1072-1087

GH therapy in PWS Adults

- **Before starting GH**
  - Genetic confirmation
  - Expert multidisciplinary evaluation
  - **Evaluation of the GH/IGF axis**
  - Treatment with rhGH must be in the context of appropriate dietary, environmental, and lifestyle interventions necessary for care of all patients with PWS

Deal et al JCEM 2013: 98(6), E1072-1087

GH therapy in PWS Adults

- **Dosing**
  - Starting dose of **0.1– 0.2 mg/d**
    - based on age, presence of edema, prior rhGH exposure and sensitivity, and concomitant oral estrogen use.
  - Subsequent dosage titration should be based on clinical response, age- and sex-appropriate IGF-I levels in the 0 to 2 SDS range.
  - IGF-I levels should be maintained within the upper part of normal range (maximum 2 SDS) for healthy, age-matched normal individuals.

Deal et al JCEM 2013: 98(6), E1072-1087

GH therapy in PWS Adults

- **Adult PWS Scandinavian Study**
  - N=46 (25 women), randomized to GH vs placebo for ONE year followed by open labelled 2 years
  - Baseline: 1/3 N BMI, 6 severe GHD, 10 IGT, 7 DM
  - At 1 year:
    - IGF-1 increased by 1.51 SDS
    - Visceral fat reduced by 22.9 ml, subcutaneous fat by 70.9 ml and thigh fat by 21.3 ml
    - Thigh muscle increase 6.0 ml
    - Lean body mass increased 2.25 kg
    - Total fat mass decreased 4.2 kg

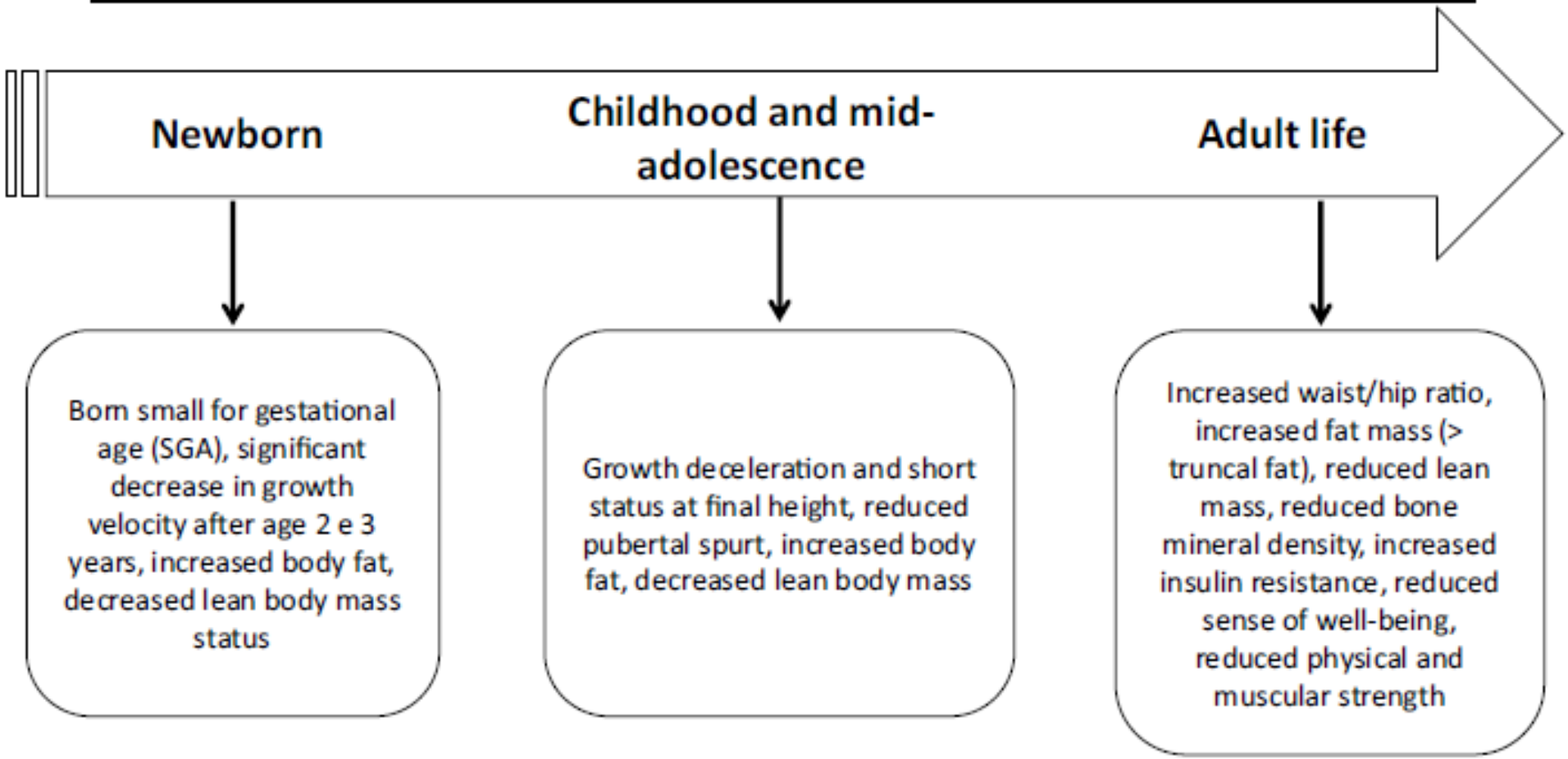
Soder-Carlsen R et al Growth Horm IGF Rese 2011; 21:185-190

GH therapy in PWS Adults

- **When to stop**
  - For adults with PWS and GHD, treatment duration depends on
    - primary clinical outcome (body composition, lipid metabolism, physical and psychosocial functioning)
    - and occurrence of side effects (impairments of glucose metabolism, edema, heart disease)

Deal et al JCEM 2013: 98(6), E1072-1087

Typical features of the Growth Hormone Deficiency in Prader-Willi Syndrome



Muscogiuri G et al Rev Endocr Metab Disord (2019)

Plan of Talk

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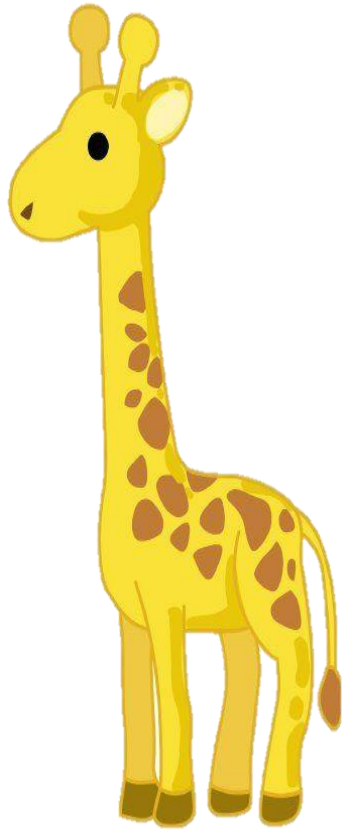
  - Adult PWS
- **Hypogonadism**
- Hypothyroidism
- Hypoadrenalism



Hypogonadism in PWS Males

- **Cryptorchidism (unilateral or bilateral)**
  - 66% to 100% of newborns
  - almost all require orchidopexy
  - Human chorionic gonadotropin (hCG) treatment has been used to:
    - lower the testicular position
    - Improve development of the scrotal sac and growth of phallus length

- **Penile length**
  - normal penile length at birth and in early childhood
  - penile length starts to fall below −2SD as they grow older

Hirsch HJ et al. Hum Reprod 2015.
Crinò A et al. Eur J Pediatr 2003
Fillion M et al. J Pediatr 2006
Siemensma EP et al. J Clin Endocrinol Metab 2012
Eiholzer U et al. J Clin Endocrinol Metab 2006
Bakker NE et al. J Urol 2015
Hirsch HJ et al. J Clin Endocrinol Metab 2009
Radicioni AF et al. Clin Endocrinol (Oxf) 2012

Hypogonadism in PWS Males

- **Puberty**
  - normal mini-puberty of infancy within the first few months of life.
  - followed by decrease in testosterone and the gonadotropins to pre-pubertal levels.
  - at the onset of puberty:
    - testosterone levels increase, but remain low
    - LH levels remain low-normal to normal
    - FSH increases and remains normal to high.
  - normal age of onset of puberty, but an arrest of pubertal progression occurs at Tanner stage 3, coinciding with testicular failure.
  - testicular size may progress to a volume of 6–7 milliliters and remain small into adulthood.
  - PWS males are generally infertile, no known reports of PWS males fathering children.
  - Inhibin B, a marker of spermatogenesis and Sertoli cell function, is low or undetectable in most adolescents and adults, which is when testicular failure is most evident.

Hirsch HJ et al. Hum Reprod 2015.
Crinò A et al. Eur J Pediatr 2003
Fillion M et al. J Pediatr 2006
Siemensma EP et al. J Clin Endocrinol Metab 2012
Eiholzer U et al. J Clin Endocrinol Metab 2006
Bakker NE et al. J Urol 2015
Hirsch HJ et al. J Clin Endocrinol Metab 2009
Radicioni AF et al. Clin Endocrinol (Oxf) 2012

Hypogonadism in PWS Males

- **Puberty**
  - No consensus exists as to the most appropriate regimen for pubertal induction or hormone replacement.
  - Dosing and timing should reflect the normal process of puberty.
  - Treatment with testosterone replacement is recommended for **PWS males with delayed or incomplete puberty**, usually **by age 15–16 years**.
  - Recommendation:
    - intramuscular testosterone replacement starting at a dose of 50–100 mg given every 28 days with gradual increase towards typical adult male doses.
  - Careful monitoring of growth and skeletal maturation.
  - Once males are at adult doses, other forms of testosterone administration can be considered including testosterone patches or gel.
  - Beware of increase risk of behavior issues and aggressive outbursts.

Gross-Tsur V et al. Reprod Biol Endocrinol 2012
Hirsch HJ et al. Hum Reprod 2015.

Hypogonadism in PWS Females

- **Puberty**
  - Up to 76% are born with hypoplasia of the external genitalia with labia minora and clitoral hypoplasia
  - Onset of puberty (breast development) typically occurs at a normal age, but
    - progression to Tanner 3 and 4 is usually delayed
    - very few reaching Tanner 5
  - Most do not progress to menarche, although 8–25% has spontaneous periods.
  - Average age of reported first period is late but varied
    - occurring at an average age of 20 years, and
    - almost all have had oligomenorrhea after menarche.

Gross-Tsur V et al. Reprod Biol Endocrinol 2012
Crinò A et al. Eur J Pediatr 2003
Eldar-Geva T et al. Eur J Endocrinol 2010.
Hirsch HJ et al. Hum Reprod 2015
Siemensma EP et al. J Clin Endocrinol Metab 2012

Hypogonadism in PWS Females

- **Puberty and Fertility**
  - Low to low-normal estrogen and LH levels.
  - FSH levels are more variable after pubertal onset (low to normal to high), indicative of mixed central and primary defects.
  - Inhibin B, a measure of gonadal function, is low in most adult.
  - A subset may have preservation of fertility.
    - Inhibin B levels >20 pg/mL correlate with the potential for fertility.
  - Six documented pregnancies
    - Females with 15q11.2-q13 deletion have a 50% chance of mothering a child with Angelman syndrome.
  - Counseling female patients on reproductive health and contraceptive practices is warranted.

Gross-Tsur V et al. Reprod Biol Endocrinol 2012
Crinò A et al. Eur J Pediatr 2003
Eldar-Geva T et al. Eur J Endocrinol 2010.
Hirsch HJ et al. Hum Reprod 2015
Siemensma EP et al. J Clin Endocrinol Metab 2012

Hypogonadism in PWS Females

- **Puberty**
  - No formal guidelines for hormone replacement in females with PWS.
  - Usual practice:
    - monitor females clinically for spontaneous initiation and progression of puberty.
    - if **no breast development occurs by age 13 years**, pubertal progression stalls, or **no menarche by age 16 years** then hormone replacement is started.
    - Oral estrogens at graduated doses are typically used for initiation or continuation of stalled puberty
    - Combined oral contraceptive pills (OCPs) are used after the first menstrual bleed has occurred.

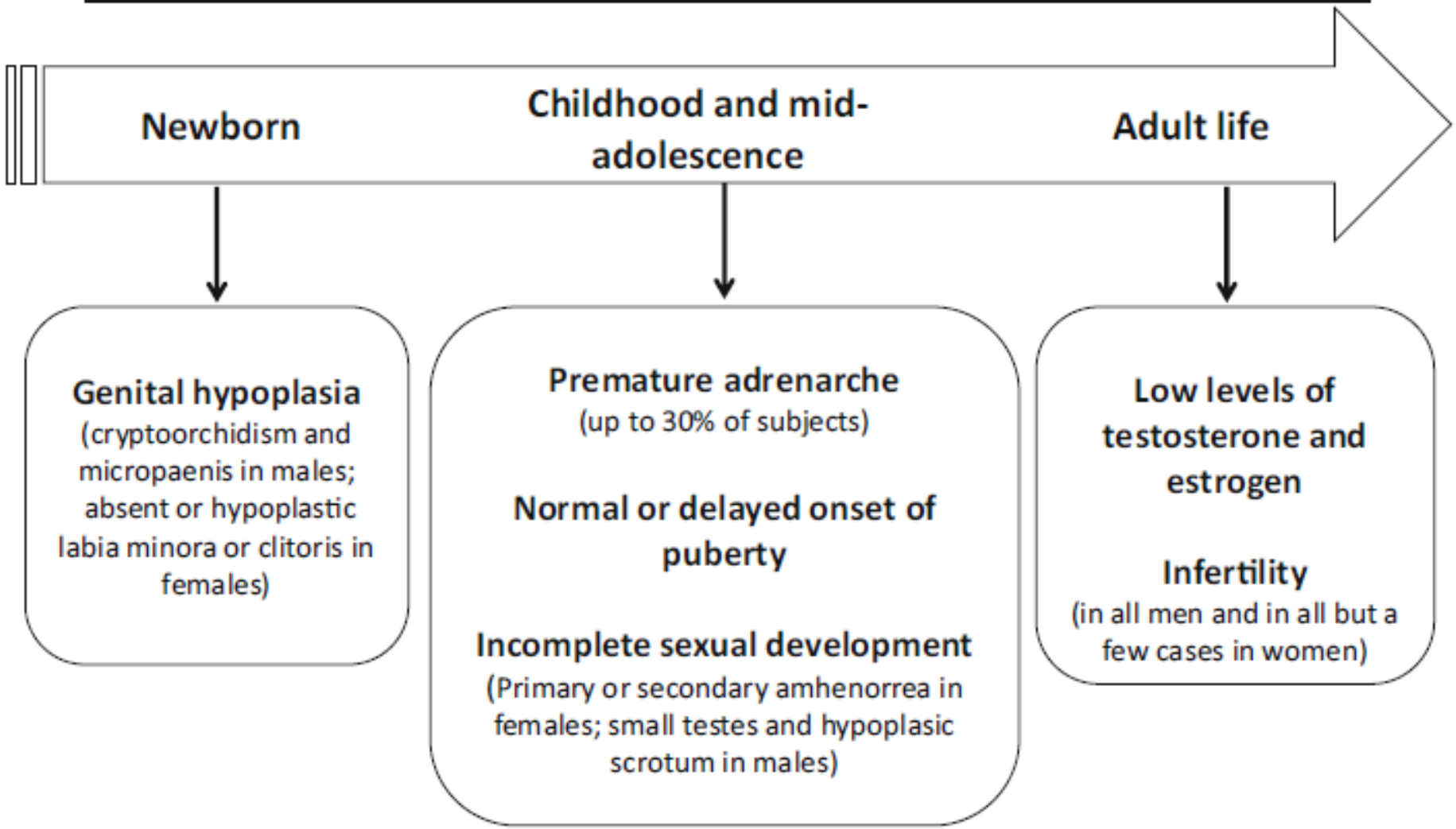
Gross-Tsur V et al. Reprod Biol Endocrinol 2012
Crinò A et al. Eur J Pediatr 2003
Eldar-Geva T et al. Eur J Endocrinol 2010.
Hirsch HJ et al. Hum Reprod 2015
Siemensma EP et al. J Clin Endocrinol Metab 2012

Hypogonadism in PWS Males & Females

- **Premature adrenarche**
  - High prevalence of 14–30%.
  - Adrenarche may be associated with advanced bone age in some cases.
  - Premature adrenarche in PWS
    - is typically not rapidly progressive or
    - associated with other signs of central puberty, and
    - is generally felt to be benign.

Crinò A et al. Eur J Pediatr 2003
Eldar-Geva T et al. Am J Med Genet A 2013
Siemensma EP et al. Clin Endocrinol (Oxf) 2011.

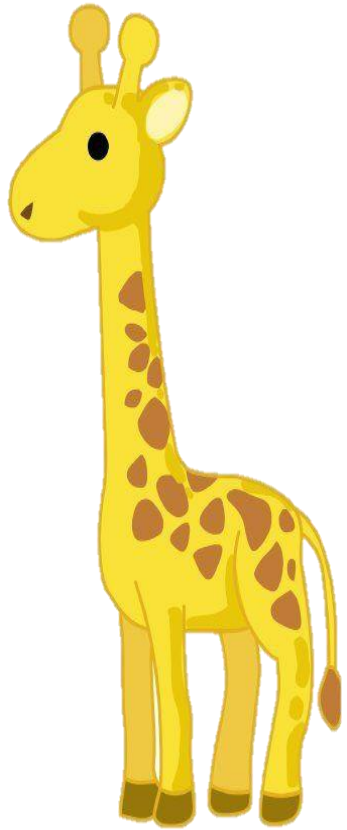
Typical development of the hypogonadic phenotype in Prader-Willi Syndrome



Muscogiuri G et al Rev Endocr Metab Disord (2019)

Plan of Talk

- Prader-Willi Syndrome
- Growth disorder
  - GH treatment in children
    - Indication/Aims
    - When to start?
    - Benefits
    - Contraindications & Warnings
    - Management Plan & Monitoring
  - Adult PWS
- Hypogonadism
- **Hypothyroidism**
- Hypoadrenalism



Hypothyroidism in PWS

- **Central hypothyroidism**
  - Hypothalamic dysfunction: increased risk for central hypothyroidism.
  - Prevalence:
    - 20–30% of patients
    - others reported low prevalence, 2–4%, no different from healthy controls or the general population.
  - No significant difference between TSH and total T4 levels on newborn screening compared to healthy controls.
  - TSH alone for newborn screens may not be enough to rule out hypothyroidism.

Butler MG et al. Am J Med Genet A 2007
Vaiani E et al. Clin Endocrinol (Oxf) 2010
Goldstone AP et al. J Clin Endocrinol Metab 2008
Sharkia M et al. J Pediatr 2013
Festen DA et al. Clin Endocrinol (Oxf) 2007

Hypothyroidism in PWS

- **Central hypothyroidism**
  - Higher rate of central hypothyroidism in the first two years of life
    - low free or total T4 levels, with normal TSH.
  - Expert consensus: to screen for hypothyroidism
    - within the **first three months of life**, and then
    - **yearly**, especially if on GH therapy (GH increase conversion of T4 to T3).
  - Treatment:
    - levothyroxine at typical replacement doses based on age and weight, if thyroid function is indicative of hypothyroidism.

Butler MG et al. Am J Med Genet A 2007
Vaiani E et al. Clin Endocrinol (Oxf) 2010
Goldstone AP et al. J Clin Endocrinol Metab 2008

Sharkia M et al. J Pediatr 2013
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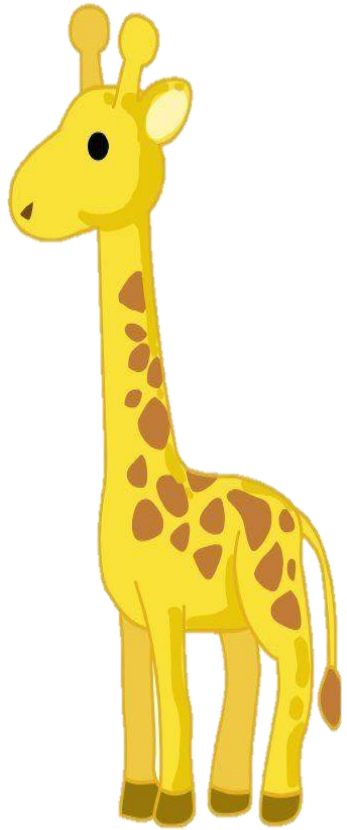

Hypoadrenalism in PWS

- **Central adrenal insufficiency (CAI)**
  - reported prevalence: 0% to 60%
  - true prevalence: unclear due to different testing methods
  - currently: no guidelines or recommendations on the appropriate evaluation and management of CAI
  - Clinicians should maintain a high index of suspicion for CAI across the life-span in PWS individuals.
  - Recommendation:
    - empiric treatment with glucocorticoids during anesthesia or major surgery
    - stress dose steroids for all patients during physical stress or illness, including mild upper respiratory infections.

Grugni G et al. Clin Endocrinol (Oxf) 2013
Nyunt O, et al. J Clin Endocrinol Metab 2010
Connell NA, et al. Clin Endocrinol (Oxf) 2010
Barbara DW, et al. J Clin Med Res 2012

Corrias A, et al. Clin Endocrinol (Oxf) 2012
Farholt S, et al. J Clin Endocrinol Metab 2011
Beauloye V, et al. Orphanet J Rare Dis 2015
de Lind van Wijngaarden RF, et al.J Clin Endocrinol Metab 2008

Hypoadrenalism in PWS

- **Central adrenal insufficiency (CAI)**
  - Good practice:
    - assess for CAI by routine testing methods prior to any major surgery or procedure requiring anesthesia
    - to treat with perioperative steroids empirically if normal adrenal function has not been documented.
  - If CAI is detected:
    - typical glucocorticoid replacement of 30–50 mg/m2/day during mild or moderate illness divided three times daily
    - and 75–100 mg/m2/dose given immediately prior to major surgery or anesthesia.
  - Caution: to avoid over treatment due to risk of obesity and poor BMD.
  - Unclear/uncertain:
    - which test is optimal for assessment of CAI
    - the need for ongoing or repeat testing over the lifetime.

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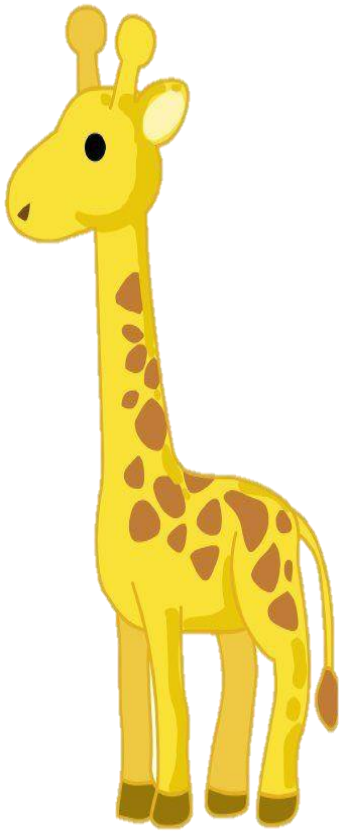
Conclusion

- GH therapy in children with PWS improves:
  - the overall physical appearance, growth (height and weight SDS), BMI (lean PWS) and strength.
  - Improves body fat, lipid metabolism.
  - No change in glucose tolerance.
- Early use of GH improves cognitive function and IQ scores.
- Pre GH and ongoing assessment is necessary to ensure healthy benefits and reducing adverse events



Conclusion

- Hypogonadism is a common finding, leading to complete or partial pubertal failure due to insufficient secretion of the pituitary gonadotropins LH and FSH, and gonadal sex steroids.
- Hypothyroidism is a common finding (approximately 20–30% of children) in PWS and it is thought to be central in origin.
- Children and adults with PWS are at risk for central adrenal insufficiency which has been detected in about 60% of cases.