

ADULT ISSUES



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Agenda

- Growth Hormone
- Other endocrinopathies
- Unique issues for adults with PWS
- Diet and exercise recommendations
- Medication trials and Supplements

Pituitary Function in Adults with PWS

- Only ~50% of adults meet criteria for growth hormone deficiency based on US Medicare standards.
- Those with PWS due to UPS have lower capacity for GH secretion than those with deletion
- Hypogonadism present in 87% of adults with PWS.
- Central hypothyroidism present in ~15% (20-25% in children).
- Central adrenal insufficiency present in ~10% of adults

Van Nieuwpoort et al, 2011; Grugni et al, 2011

Growth Hormone for Adults with PWS



Available Data on GH in Adults with PWS

- There have been 10 studies of GH in adults with PWS. Stimulation test is typically GHRH/arginine test. GH response low in up to 50%.
- 8 studies have evaluated results of GH treatment in PWS (2 RCT). Average GH dose in adults 0.6 mg per day on average in all studies.
- Left ventricular mass increased in some with GH treatment.
- Most common side effect of adult treatment was edema.
- Insulin and glucose levels increased during treatment. Few had headache and myalgia. 6/38 adults had progression of scoliosis.

IGF-1 Levels

- IGF-1 levels are surrogate marker for GH levels
- Recent studies show IGF-I levels <-2 SDS in 47% of adult patients with PWS
- IGF-I levels correlate with self-assessment of quality of life, IQ scores, and appetite assessment in adults with PWS.
- However, studies have shown that response to GH therapy in adults is unrelated to either peak GH stimulatory response or to baseline IGF-I levels – all adults with PWS have improvements in body composition on GH therapy.

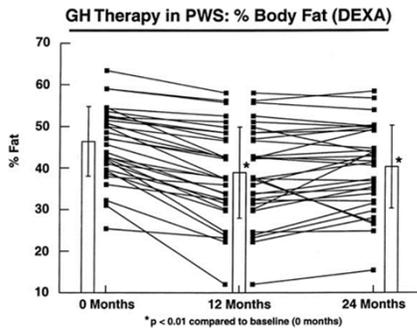
Van Nieuwpoort et al, 2011; Sode-Carlson et al, 2010

So...to treat or not to treat with GH?

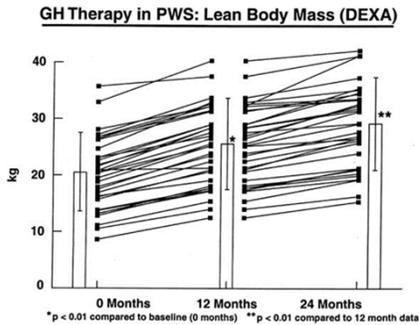
- Upcoming guidelines for GH treatment in PWS will recommend that all adults undergo GH stimulation testing prior to starting GH.
- Those that pass stimulation testing cannot get GH in the US.
- Evidence shows that benefits from GH treatment are present regardless of GH status prior to treatment.
- Contraindications to GH therapy in adults with PWS are morbid obesity, severe untreated obstructive sleep apnea.



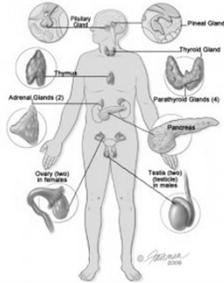
Changes in fat mass with GH treatment in adults with PWS



Changes in muscle mass with GH treatment in Adults with PWS



Other Endocrinopathies Commonly Seen in PWS



Central Adrenal Insufficiency

- Adrenal insufficiency can result in low blood pressure, low blood sugar, and sudden death during times of stress/illness.
- First study in 2008 by Dutch group indicated 60% of individuals with PWS have CAI using metyrapone stimulation testing.
- Subsequently 3 other studies have showed 0% using high and low dose ACTH stim testing.
- We found approximately 10% of our patients have CAI using glucagon stimulation testing, with prevalence highest in infants and adults.
- Tauber (France) and Goldstone (UK) found 10% using gold standard testing.

Adrenal insufficiency (continued)

- Testing is unreliable and inconsistent, except insulin tolerance testing.
- We recommend treating with hydrocortisone as if patients have adrenal insufficiency if they are in ER, ICU, surgery, motor vehicle accident, or significantly ill if adrenal sufficiency status is unknown.

Bone Problems

- Osteoporosis/osteopenia present in 96% of adults with PWS
- Many do not get enough calcium/Vit D in diet due to low-cal diets
- High pain tolerance
- Scoliosis present in 45% of adults with PWS
- High incidence of congenital hip dysplasia – often not recognized and untreated in infants/young children with PWS, so leads to significant issues, including pain and abnormal gait in adults.

Type 2 Diabetes Mellitus

- Rarer than expected for degree of obesity, due to more subcutaneous than visceral fat accumulation.
- Very obese (BMI >35) have 27% diabetes.
- Adults with PWS have increased insulin sensitivity, elevated ghrelin, and decreased insulin secretion.
- The addition of GH therapy worsens insulin resistance, but no studies have found that GH treatment pushes people with PWS into the development of diabetes.



Hypogonadism

- Hypogonadism was always thought to be central in nature due to presumed hypothalamic dysfunction in PWS.
- Recent studies show that the hypogonadism: a) can be central due to pituitary dysfunction ;or b) due to early primary gonadal dysfunction (testicular/ovarian damage); or c) combined hypogonadism.
- Treatment is the same regardless of the cause, but is important to know the cause, when possible, to determine if future fertility is a possibility or not.

Radicioni et al, 2011.

Treatment for hypogonadism

- Menarche typically occurs in late 20-40's, if at all, and often is only intermittent spotting.
- Combination estrogen/progesterone therapy is typically started for women at puberty, although there is still question about the necessity.
- There is more controversy about when to initiate hCG or testosterone therapy for males.
- In general, there is controversy about whether to treat adults with hormone replacement as anecdotal evidence suggests worsening of behavioral problems/psychosis.

Unique Issues for Adults with PWS



Psychiatric Problems

- Individuals with PWS are at high risk for developing mood disorders with or without psychosis.
- Those with UPD at higher risk for psychosis than those with deletion.
- Prodromal phase of psychosis includes: physical complaints: fever, enuresis, headaches, vomiting, gastro-enteritis. Few days later have florid psychosis: delusions, anxiety, hallucinations. Few days later go into phase of catatonia (sleeping a lot, refuse food), then few days later go back to hyperactive state. (constant swing from hyperactivity to hypoactivity).
- Effect of GH unknown on the development of process of psychosis unknown.

Behavioral Issues



- Age-related increases in many symptoms those in their twenties have consistently highest behavioral issues.
- Remarkable drop in severity and frequency of symptoms in middle adulthood
- Type I deletions: behavior seems to mellow- fewer behavior problems-less repetitive, easier to redirect, less tantrums and may even lose weight as they age.
- Type II deletions: behavior seems to be more stable over time.

Self-Injurious Behavior

- Skin picking becomes very common when individuals with PWS enter insatiable appetite phase.
- Often will develop sores that will not heal for many months, with subsequent infections.
- Topamax or N-acetylcysteine have shown promise in treating skin picking behaviors

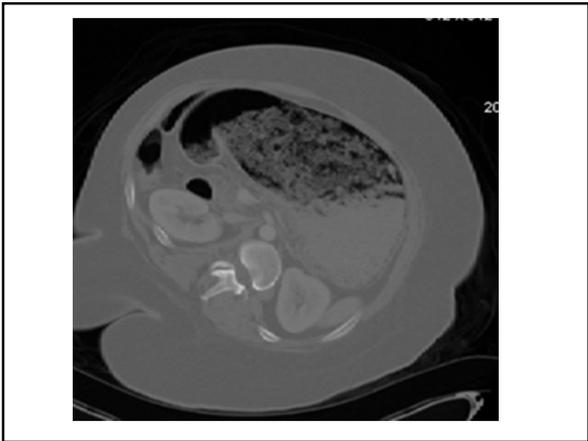


Gastric Dilation

- Gastric dilation/necrosis can occur if teens/adults eat large volumes of food quickly especially after period of dietary restriction.
- It is thought that the muscles of the stomach had become atonic and atrophied after a period of strict dietary control in PWS.
- This atrophy of the stomach muscles, along with the lack of vomiting and lack of feedback of sensation of fullness from stomach to brain, and the delayed gastric emptying is what causes the stomach to become massively dilated and rupture when large amounts of food are ingested.

Gastric Dilation/Necrosis

- The stomach wall will stretch as far as possible to accommodate large volumes of food, but the increased pressure on the walls of the stomach will cause the inner stomach wall to tear, pushing air into the veins of the abdomen.
- With enough pressure or enough volume of food, the entire stomach wall (both inner and outer layer) will tear and gastric contents will go into the abdominal cavity causing massive infection, organ failure, and death.



Sleep Issues



Sleep Disturbances in PWS

- Individuals with PWS are at increased risk for obstructive sleep apnea, central sleep apnea, and hypoventilation.
- Obesity worsens sleep disturbances – primarily obstructive sleep apnea.
- CPAP is often recommended but compliance is poor
- GH seems to improve both central and obstructive sleep apnea in individuals with PWS

Excessive Daytime Sleepiness

- Many patients with PWS have excessive daytime sleepiness unrelated to sleep apnea.
- Symptoms typically will meet criteria for narcolepsy without cataplexy.
- Several adults have drowned in the bathtub likely due to excessive daytime sleepiness
- Provigil helps many individuals with daytime sleepiness. Other stimulants worsen skin-picking or cause tics.

Diet and exercise recommendations



Our goal is to treat or prevent obesity in adults with PWS

Obesity in PWS

- Individuals with PWS have less muscle mass and increased fat mass from infancy.
- Without GH treatment in childhood, this continues to worsen as they age.
- As adults diet must be limited to 60-70% of caloric intake recommended for a typical adult.
- Exercise must be done daily 30-45 minutes per day.
- Recommend diet that is 30% fat, 45% carbohydrates, and 25% protein with 20 grams of fiber per day, which works well to prevent obesity.

Exercise

- Recommend daily exercise for 30-45 minutes per day of aerobic exercise.
- Weight lifting is wonderful for helping bone strength and muscle mass, as well as weight control when used in conjunction with aerobic exercise.
- Will often give caloric rewards for exercise – 100 calories for 30 minutes of aerobic exercise and 150 calories for 45 minutes.

Exercise Recommendations

Targets for Treatment of various aspects of PWS

- Oxytocin (appetite, behavior)
- Byetta???? (appetite)
- Medications which target hypothalamic satiety centers
- Hypothalamic stimulation (appetite, weight)
- Transcranial magnetic stimulation (behavior)
- Gastric nerve stimulator (appetite)

Oxytocin and Byetta Studies

- Oxytocin study done in France: 1 spray of oxytocin given to adults with PWS – improved social skills, emotional recognition, and possibly appetite.
- Byetta study done in Australia: improvement in gut hormones of satiety (insulin, GLP-1, and PYY) and decreases in subjective hunger measurements
- Satiety based on appetite rating scales – appetite itself not actually tested, so unclear if it will actually decrease the amount of food ingested.
- Since it further delays gastric emptying, which is already delayed in PWS, there is an even higher risk for gastric dilation/necrosis if large amounts of food are consumed after taking this medication.

Supplements

- Carnitine – up to 30% of adults with PWS have carnitine deficiency in our clinical practice. Carnitine supplementation helps improve daytime alertness.
- Coenzyme Q10 – up to 20% of adults deficient, and can help with daytime alertness.



Supplements (continued)

- Melatonin to help regulate circadian rhythm
- Vitamin D – unclear how many are deficient, but everyone needs to be checked annually, during winter, and supplemented if low (vitamin D deficiency is associated with osteoporosis and also linked to autoimmune disorders).

Questions?
