Human chorionic gonadotropin (hCG) for Improved Virility without Negative Behavioral Changes in Hypogonadotropic Hypogonadic Adolescent Males with Prader-Willi Syndrome

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Abstract

Background: Prader-Willi Syndrome (PWS) is a rare genetic, metabolic disorder affecting both males and females equally. Along with compulsive and gluttonous eating, affected youth also suffer from varying degrees of mental retardation and decreased sexual development. Being physically underdeveloped as compared to their peers may make children suffering from PWS more self-conscious, and more likely to suffer from behavior disturbances. Studies have shown some positive response to exogenous administration of human chorionic gonadotropin (hCG) in the stimulation of sex hormones as well as development of secondary sex characteristics. Traditional treatment with testosterone has led to increased aggression, and exacerbation of PWS behavioral disturbances. hCG has been shown to improve virility in male patients, without the negative behavioral effects seen in testosterone treatment. To this point, only case studies and anecdotal evidence have been available. Could the lives of youth suffering from this disorder be improved with carefully timed administration of hCG?

Methods: An exhaustive search of the literature was conducted using Medline/OVID, NCBI/PubMed, Web of Science, and CINAHL using the key words: Prader-Willi Syndrome, and hCG. Relevant articles were assessed for quality using GRADE. There are no currently registered NIH clinical trials involving the treatment of hypogonadal peripubertal PWS patients with hCG.

Results: Two studies met inclusion criteria for this systematic review. Two clinical follow-up studies involving 6 study subjects treated with hCG injections demonstrated improved sexual maturity (as evidenced by improved testicular volume and secondary sex characteristics) and hormonal normalization with no significantly concerning behavioral changes.

Conclusion: hCG has been shown to improve secondary sex characteristics and hormonal levels without negative behavioral changes in peripubertal male patients when managed by a pediatric endocrinologist. More research is needed to determine comparisons with other existing and potential treatments, including depo-testosterone, etc. Improved studies (including RCTs) and study designs could also further improvements in the management of PWS-hypogonadism. Challenges include the global rarity of the disease, and finding enough subjects to provide adequate study populations.

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First Advisor
Mark Pedemonte, MD

Keywords
Prader-Willi Syndrome, hCG (human chorionic gonadotropin), hypogonadism

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Human chorionic gonadotropin (hCG) for Improved Virility without Negative Behavioral Changes in Hypogonadotropic Hypogonadic Adolescent Males with Prader-Willi Syndrome

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A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR

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ABSTRACT

Background: Prader-Willi Syndrome (PWS) is a rare genetic, metabolic disorder affecting both males and females equally. Along with compulsive and gluttonous eating, affected youth also suffer from varying degrees of mental retardation and decreased sexual development. Being physically underdeveloped as compared to their peers may make children suffering from PWS more self-conscious, and more likely to suffer from behavior disturbances. Studies have shown some positive response to exogenous administration of human chorionic gonadotropin (hCG) in the stimulation of sex hormones as well as development of secondary sex characteristics. Traditional treatment with testosterone has led to increased aggression, and exacerbation of PWS behavioral disturbances. hCG has been shown to improve virility in male patients, without the negative behavioral effects seen in testosterone treatment. To this point, only case studies and anecdotal evidence have been available. Could the lives of youth suffering from this disorder be improved with carefully timed administration of hCG?

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Key words: Prader-Willi Syndrome, hCG (human chorionic gonadotropin), hypogonadism
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LIST OF ABBREVIATIONS

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<th>Description</th>
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<tr>
<td>PWS</td>
<td>Prader-Willi Syndrome</td>
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<td>hCG</td>
<td>human chorionic gonadotropin</td>
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<tr>
<td>BA</td>
<td>Bone age</td>
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<tr>
<td>CA</td>
<td>Chronological age</td>
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<tr>
<td>GH</td>
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<tr>
<td>LH</td>
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<td>FSH</td>
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<td>WFH</td>
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Human chorionic gonadotropin (hCG) for Improved Virility without Negative Behavioral Changes in Hypogonadotropic Hypogonadic Adolescent Males with Prader-Willi Syndrome

BACKGROUND

Prader-Willi Syndrome (PWS) is a rare genetic, metabolic syndrome affecting both males and females equally, caused by a faulty expression of the paternal PWS segment on chromosome 15q11.2-q13. Diagnosis is confirmed with genetic testing generally in response to abnormal infantile development. Prevalence in the United States is approximately 1:15 000-25 000, with roughly 400 000 individuals affected worldwide. Treatment efficacy is closely related to the age of diagnosis, but due to the rarity of the syndrome PWS can often be missed by pediatricians and primary care providers. PWS patients suffer with compulsive and gluttonous eating, varying degrees of mental retardation, specific physical dysmorphisms and late or decreased sexual development. Human growth hormone (GH) was approved by the FDA for treatment of PWS in 2000, and has been shown to improve lean muscle mass, bone density abnormalities, and normalize height, but fails to correct hypogonadism and subsequent sequelae.

Hypogonadism can usually be attributed to various degrees of hypothalamic dysfunction. Much evidence points to a deficit in the hypothalamic-pituitary-gonadotropin axis in boys with PWS, but there are also elements of primary hypogonadism. Hypothalamic disorders may be suggested with low leutinizing hormone (LH). Primary failure involving the testes generally demonstrates low inhibin B and high follicle-stimulating hormone (FSH) levels, indicating a defect in Sertoli and/or germ cell maturation or an early germ cell loss. Testicular histology also varies significantly, with cryptorchidism being much more common in PWS males.
Hypogonadism found in PWS has been historically difficult to study as the endocrine component of the disease state is complicated, paired with the relative rarity of the disease. Most articles identified in the literature focus on individual case studies or small groups of patients and lack the depth and clinical significance of randomized control trials or other robust study designs. The specific components of the hypothalamic hypogonadic aspect of the disease are better understood now, but treatment plans are still generally determined by individual endocrinologists without well-defined standard guidelines.

Testosterone undecanoate is the FDA-approved medication for use in primary hypogonadism, as well as hypogonadic hypogonadism in male patients. Improved virilization and balance of serum hormone levels are common using testosterone treatments, however adverse drug reactions including mood swings, agitation, irritability, and insomnia are frequently found. Increases in serum testosterone levels were inconsistent, as has been the regulation and normalization of FSH and LH.

Another hormone to consider in treating hypogonadism is hCG, however, previous studies have noted varied response to therapy with hCG in hypogonadic patients without PWS. Furthermore, there has been hesitation to treat PWS patients with exogenous sex hormones, like testosterone and hCG, over concerns that therapy frequently exacerbates pre-existing problems found in PWS patients. hCG treatment in PWS patients allows for improved control and adjustment of dosing preventing major fluctuations of testosterone, as hCG stimulates testicular development and subsequent release of endogenous testosterone and other sex hormones as well as development of secondary sex characteristics. To this point, only case studies and anecdotal evidence have been available.
Exogenous administration of hCG has potential to improve the symptoms of PWS, without the high adverse drug reaction profile commonly found in treatment with exogenous sex hormones. Medication can be carefully titrated to avoid adverse effects, and have more regulated therapeutic response. Studies involving treatment with hCG are limited, but show promise. More studies involving larger populations of subjects are vital to improving the lives of these patients. Could the administration of exogenous hCG in the treatment of Prader-Willi Syndrome-associated hypogonadism improve virility, behavior, and secondary sex characteristic presentation in peripubertal male patients?

METHODS

An exhaustive search of the available literature was conducted using Medline/OVID, NCBI/PubMed, Web of Science, CINAHL and the key words: Prader-Willi Syndrome, and hCG (human chorionic gonadotropin). The search was narrowed by including English language articles involving adolescent male subjects. Abstracts were reviewed, with relevant articles being reviewed in their entirety. Bibliographies of pertinent articles were reviewed. Relevant articles were assessed for quality using the GRADE criteria (Grading of Recommendations, Assessment, Development, and Education).\textsuperscript{10} There are currently no registered NIH clinical trials involving the treatment of hypogonadic peripubertal PWS patients with hCG.

RESULTS

The initial result of the search including "Prader-Willi Syndrome" with "Chorionic Gonadotropin/hcg" yielded 191 articles for review in the English language. After careful review of these articles, 16 met the inclusion criteria for primary data involving human subjects. As PWS-related hypothalamic hypogonadism is such a unique disorder among other metabolic genetic diseases, articles included were limited to those dealing with PWS-specific
hypogonadism being treated with hCG, excluding other forms of hypogonadism. These articles were narrowed down to two "clinical follow-up" studies.\textsuperscript{9,11} See Table I.

**EIHOLZER et al (2006)**

This study is described as a “clinical follow-up” study with the intent to investigate the cause of PWS hypogonadism as well as determine whether the exogenous administration of hCG at pubertal failure can restore development and Leydig cell function. Patients were divided into two samples; 8 infants and 6 peripubertal boys. The study was conducted over 1.5 years and 4.5 years (respectively) at the Institute Growth Puberty Adolescence, a pediatric endocrine specialty center in Zurich, Switzerland. All study subjects had genetically confirmed PWS at the time of enrollment in the study. Considering ethical limitations, the study was observation only, with no specific age-matched control group.\textsuperscript{11}

The infants initially had normal values for serum testosterone, LH, and inhibin B, but increased FSH as compared to age-appropriate reference range. However, testosterone, LH, inhibin B, and FSH all began to gradually decline between the ages of 5 and 18 months. Values were analyzed for differences between boys with normally descended testicles as compared to those with either unilateral or bilateral cryptorchidism. No differences in hormonal values were noted in those children with normally descended testes as compared to those with maldescent. Infants were given daily injections of recombinant human GH (Genotropin); 6 mg/m\textsuperscript{2} weekly, beginning therapy at 6 months (n=2), 12 months (n=3), and 18 months (n=3).\textsuperscript{11}

The primary outcome studied in the adolescent participants (n=6) was gonadal function prior to and during puberty. Subjects were retrospectively analyzed every 6 months from 10-17 years of age. At each visit patients were measured for height and weight, Tanner pubertal staging, and testicular volume. The boys were X-rayed to determine bone age every 12 months,
whereas pubertal boys were scanned every 6-9 months. Serum FSH, LH, inhibin B, and testosterone levels were drawn and compared to age-dependent values of comparable reference ranges. Serum IGF-I levels and height had previously been normalized using standard human growth hormone therapy. Twice weekly intramuscular (IM) hCG injections were initiated for bone ages 13-16 years at evidence of pubertal arrest, mean age 13.9 years. Pubertal arrest was determined by stabilization of testicular volume around 4.0 ml, additional lack of testosterone increase, and bone maturation. Most had full pubic hair development (Tanner Stage 5) at pubertal arrest. Inhibin B levels were below normal, LH and testosterone levels were in the lower normal range until age 13 years. There was 500 U of hCG administered to boys with bone age 13-13.5 years, 1000 U hCG administered to 13.6-14.5 years, and 1500 U for boys older than 14.5 years.\textsuperscript{11}

Treatment with hCG improved Leydig cell response; increasing serum testosterone 2.8 fold to low-normal levels, reducing FSH levels 3 fold, and maintaining LH levels. However, even with an increase in testosterone level, there failed to be an increased secretion of inhibin B. The authors concluded that this most likely indicates a Sertoli cell dysfunction of tubular origin, which could not clearly be explained by the cryptorchidism commonly found in most male PWS patients. Testicular biopsies of descended testes demonstrated absent germ cells, indicating a probable primary gonadal defect, combined with a hypothalamic deficit causing the peripubertal failure of LH increase in patients with PWS.\textsuperscript{11}

Physical characteristics improved significantly with genitals increasing to low adult size, and the deepening of the voice. Most importantly; treatment with hCG led to an increase in testosterone and secondary sex characteristics without significant negative behavioral response. No increase in social or behavioral problems was noted during hCG treatment. The authors
suggest substitution with sex hormones at puberty for the normalization of pubertal development. No advances were made towards the restoration of spermatogenesis.\textsuperscript{11}

**EIHOLZER et al (2007)**

This study\textsuperscript{9} aimed to demonstrate the utility of sex hormone replacement therapy on male adolescent patients with PWS, in addition to GH therapy. Primary goals of the study were to "complete male pubertal development in a physiological, well-balanced and cautious way." The study is described as a clinical follow-up study with the intent to evaluate the effects of exogenous hCG on pubertal boys with PWS-associated hypogonadism. Six hypogonadal peripubertal boys with genetically confirmed PWS were followed for a minimum of two years, prior to and following pubertal arrest. All boys were already undergoing long-term treatment with human growth hormone (GH). Patients were treated with hCG 500-1500 IU IM twice weekly and evaluated every six months from age 7 to 17 years. Examinations evaluated height, weight, growth velocity per year, Tanner Stage of pubertal development, testicular volume, chronological and bone age, body composition, testosterone levels, and behavior. Questionnaires were administered to the parents, considering their perceived changes in the patient in question, and when possible, compared to siblings with normal onset puberty. The questionnaire addressed (1) relations to peers; (2) sexuality; (3) aggressiveness; (4) preoccupation with one's own appearance; (5) risky behavior; (6) retraction from social interaction; (7) mood, and (8) school performance, subdivided into a total of 19 items. Considering ethical limitations, the study was observation only, with no specific age-matched control group.\textsuperscript{9}

Prior to treatment with hCG, bone age and pubic hair development was slightly accelerated. Puberty started at a mean age of 11.2, with arrest occurring at 13.5 years as determined by bone maturation, cessation of voice deepening and testicular growth, and
stabilization of serum testosterone levels. Administration of exogenous hCG led to increased and sustained rises in testosterone to low-normal levels, development of Tanner stage 5 pubic hair pattern, linear growth velocity increases, as well as deepening of the voice. Testicular volume increased mildly, but remained in the small to small-normal range. Lean mass and testosterone levels both increased in boys treated with hCG, and became either normal or low normal in 4 out of 5 boys. Fat mass and BMI remained elevated, but stabilized at 38%, considerably lower than other PWS adolescent boys without treatment.\(^9\)

Behavioral and mood disturbances common in adolescents with PWS were divided into three main categories; (1) difficulties in or lack of social interaction; (2) aggressiveness or interpersonal conflicts; and (3) irritability or rapid mood changes. Of these three categories, patients being treated with hCG identified with problems with social interactions were found to not worsen in 3/6 patients, and improved in 2. Aggression worsened in 3/6 patients, but was similar to increases in aggression of 3 of 5 pubertal brothers unaffected with PWS. In this same category, aggressive behavior outside of the family unit decreased in 4/6. Three of six patients had PWS-related irritability that was considered greater than siblings without PWS, but was not considered altered during therapy. Sexuality and sexual arousal was less of a problem in patients with PWS, and were less difficult in patients when treated with hCG.\(^9\)

The authors concluded that exogenous hCG improves pubertal development and muscle mass, without the negative behavioral components found in patients treated with exogenous testosterone and other sex hormones. Treatment with hCG did not appear to increase problematic behaviors, including relations with peers, sexuality, aggressiveness, participation in risky behaviors, social retractions, or irritability. However, knowledge that their children were being treated with hCG may have introduced bias, potentially affecting the way in which parents
answered the behavioral questionnaire. Treatment with hCG did appear to improve growth velocity in boys without spontaneous growth spurts, however, patients were not able to generate viable sperm, and testicles did not achieve a volume greater than 6 ml. Researchers suggest initiation of sex hormone in PWS with hypogonadism at pubertal failure, or 13-14 years of age.

Future research regarding increased adolescent psychotic episodes in PWS patients being treated with sex hormones is recommended by the authors of this study. It is unclear if hCG treatment leads to similar increases in psychotic deterioration as found with testosterone treatment. Comparisons between therapy with hCG and testosterone are also recommended, especially including larger study and control groups.

**DISCUSSION**

Hypogonadism in boys with PWS stems from poorly understood hypothalamic and gonadal failure. Infants identified with severe hypotonia and poor feeding can be confirmed to have PWS via genetic testing. Treatment for PWS generally begins in infancy with regular administration of GH to normalize body mass and skeletal growth. PWS patients have a form of hypogonadism that is specific to this syndrome, and is unique compared to other hypothalamic hypogonadic disorders. Infants generally present with normal serum levels of LH and testosterone, but gradually declining inhibin B levels and rising FSH, fail to complete adult sexual development. Administration of sex hormones including testosterone has been shown to improve sexual development and maturity, but often have undesired behavioral effects. As demonstrated by these two studies, hCG is an alternative therapy that may combine the desired therapeutic benefits of androgens, without the adverse drug reactions. hCG has been used successfully in treating patients with other forms of hypogonadism including hypopituitarism and hypogonadotropic hypogonadism and holds potential in treating patients with PWS.
When combined with traditional GH therapy, hCG improves virilization, hormone profiles and has less negative behavioral effects than treatment with testosterone. While there have been promising case studies, and small group clinical observation studies, results are generally not complete enough or lack evidence to include in approved treatment regimens. Further research into better understanding the origins of the endocrine dysfunction and specific treatments for PWS are important, however unlikely due to the rarity of the syndrome, and the lack of rigorous clinical studies.

Research in this field is limited. Studies have been completed regarding various hypothalamic, hypogonadotropic, and hypogonadic disorders, but the actual etiology of PWS is poorly understood. Both studies\textsuperscript{9,11} involved a very small group of adolescent boys with PWS. Eiholzer et al (2006)\textsuperscript{11} and Eiholzer et al (2007)\textsuperscript{9} both indicated that the use of hCG can be as effective as testosterone undecanoate when used in the treatment of hypogonadism of PWS boys, however, both studies demonstrate significant limitations. Both were described as “clinical follow-up” studies, clearly lacking blinding and randomization. While treatment effect may be measured, without comparable control values, it is difficult to confidently determine the success of therapy. It was also noted that questionnaire answers might have been influenced by parents’ knowledge that their child was being treated with a medication hoped to reduce negative behaviors. See Table I.

The treatment of PWS patients is complex, and frequently beyond the realm of the typical primary care provider. Patients are best managed in a team approach utilizing primary care, pediatric endocrinologists, behavioral and mental health specialists, dieticians and social workers. The role of the family provider should be one of support and management of the whole patient. Decisions to start a patient on hormone therapy should be a conversation between the
provider and the patient’s parents at diagnosis of PWS, as well as arrival at puberty. Benefits and potential risks of therapy should be clearly and carefully enumerated. Initiation of therapy should involve an endocrinologist, preferably with experience treating children with PWS or other hypogonadic disorders. Treatment with hCG should be included in the conversation, frankly discussing known advantages and disadvantages.

At this time, treatment of PWS hypogonadism with hCG can be considered, but it is too soon to recommend it over other existing treatments. More research is needed in this area to better understand the effect of therapy, as well as the advantages over other existing medical treatments. hCG may be more appropriately reserved for patients who have intolerable adverse reactions to other medications. There exists little in the literature focusing on the specific PWS picture, and treatments appropriate for this form of hypogonadism. While more research would undoubtedly lead to better management, the low prevalence makes PWS a low-priority and difficult task in the research world. Ideally, future research would involve improved study designs involving larger populations, blinding and randomization, as well as comparisons between existing treatments, hCG, and control groups.

CONCLUSION

Treatment of hypogonadic PWS boys with hCG has been shown to improve the symptoms associated with a poorly functioning pituitary-hypothalamic axis. Growth hormone improves lean muscle mass as well as linear growth and bone development, however, treatment with testosterone and other sex hormones has been indicated to complete pubertal development. Androgens have been implicated in development and exacerbation of behavioral problems. While hCG treatment appears to have a similar effect on improvement of pubertal development and secondary sexual characteristics as testosterone, it appears to lack the negative behavioral
profile found with patients treated with testosterone. This data is limited by the lack of good study designs and subject populations. Existing research is lacking in clinical strength, owing to it’s mostly observational and anecdotal nature. More is needed to better understand the causes of PWS hypogonadism, and to direct further research and treatments. Determining the efficacy of hCG as compared to testosterone, and to include it in standard PWS endocrine therapy in adolescent boys may still be forthcoming. Randomized controlled studies involving larger populations are crucial for evaluation. There is ample opportunity for research into this rare disease, and strong clinical evidence can only further illuminate the benefits of treatment with hCG.
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TABLE I. Characteristics of included studies, GRADE evidence profile: hCG for hypothalamic hypogonadic adolescent boys with Prader-Willi Syndrome

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Downgrade Criteria</th>
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<tr>
<td>Design</td>
<td>Limitations</td>
<td>Indirectness</td>
</tr>
<tr>
<td>EIHOLZER et al (2006)¹¹</td>
<td>Observational</td>
<td>Very Serious*</td>
</tr>
<tr>
<td>EIHOLZER et al (2007)⁹</td>
<td>Observational Followup</td>
<td>Very Serious*</td>
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Abbreviations: GRADE: Grading of Recommendations, Assessments, Development and Evaluation.

a. Both studies focused on the same experimental group of 6 peripubertal boys, no control group was specifically identified and both studies lack a control group

b. Both studies have a very small, identical n of 6