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Literature Review Of Early And Precocious Puberty In Girls

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### **Problem**

Early/precocious puberty, while a relatively rare condition, occurs in approximately 20 per 10,000 girls. Girls outnumber boys in precocious puberty by a three to one ratio (Steelman, 2011). Approximately 4-5% of girls will go through precocious puberty (Shapiro, 2013).

Early/precocious puberty can present with either signs of adrenarche (increased hormones in the body), thelarche (breast development, most common first sign), pubarche (appearance of pubic hair), or menarche (menstruation). With early pubertal timing girls have an increased risk of being treated differently by adults, with expectations to behave at the age of their outward appearance instead of their chronological age. Early pubertal timing increases the female's risk of sexual abuse, obesity, cardiovascular disease, short adult stature, behavioral problems, breast cancer due to longer estrogen exposure over their lifetime, and risk taking behaviors such as alcohol and drug abuse as well as teen pregnancy.

The ages to define the onset of puberty, precocious puberty, and early puberty are debatable within the medical community. The average age of puberty in girls is 10 to 14 years old (MedLinePlus, 2013). Precocious puberty is defined as the onset of secondary sexual characteristics before age 7/8 years in Caucasian girls and 6 years old in African American girls (Mayo Clinic, 2013). Additionally, menarche before 9 years old is indicative of precocious puberty (Mercola, 2012). Early puberty would be characterized as secondary sexual characteristics between 8 and 10 years old, although some define early puberty as less than 12 years for research purposes. It is more commonly found in girls, with African American girls maturing on average one year earlier than their Caucasian/Hispanic counterparts.

The pituitary gland, which regulates hormonal production and ovarian stimulation, starts producing hormones early leading to the development of secondary sexual characteristics

(University of Michigan Health System, 2013). For girls, the increase in estrogen levels stimulates breast enlargement (Tanner stage 2) in girls and is usually the first sign of puberty. However, in some cases menarche (menses) or pubarche (pubic hair) can appear first. Additionally, there is an increase in skeletal maturation, leading to an initial early height increase. However, final height in early/precocious puberty girls is usually less than their on-time/late puberty counterparts (Shapiro, 2013).

Precocious puberty can be divided into the following: central precocious puberty, or gonadotropin dependent (usually idiopathic) and peripheral precocious puberty, or gonadotropin independent (caused by increased estrogen in the body). GnRH testing can help distinguish between the two. Central precocious puberty, or idiopathic precocious puberty, is the most common. It is caused by early maturation of the Hypothalamus-Pituitary-Gonadal (HPG) axis. For central-type puberty to occur, there must be a functioning GnRH neuronal network and pulsatile GnRH secretions, caused by tonic inhibitory restraints (GABA receptors) and excitatory inputs (amino acid glutamate) to the GnRH neurons. The GnRH secretion mechanisms are located within the neuronal and glial networks (Partsch & Sippell, 2001). With HPG, the hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones cause the ovaries to produce estrogen, which influences the development of secondary sexual characteristics. Although there is usually no identifiable cause in 69% to 98% of girls with central precocious puberty it may be caused by the following: tumor in the brain/spinal cord, defect at birth such as hydrocephalus or hamartoma (noncancerous tumor), radiation or injury to the spinal cord, McCune-Albright syndrome, congenital adrenal hyperplasia, or hypothyroidism (Mayo Clinic, 2013).

Peripheral precocious pubertal development is due to premature excretion of sex steroids from the ovaries, adrenal glands, pituitary, or exogenous exposure. This type of pubertal development originates peripherally, not centrally at the GnRH pulse generator, and will have low responses to GnRH stimulation (Partsch & Sippell, 2001). Additionally, the following may lead to precocious puberty: estrogen-secreting tumor of the adrenal glands or pituitary gland, McCune-Albright syndrome, and exposure to external sources of estrogen such as lotions/creams/ointments (Mayo Clinic, 2013).

Possible causes of early or precocious puberty can include problems with the adrenal gland or ovaries. While there is debate among the medical community on when to test and treat for early/precocious puberty, providers must contemplate ruling out possible causes for early pubertal onset by evaluating for tumors and endocrine disorders (diabetes, polycystic ovarian syndrome, etc.). Obesity, environmental hazards, and social factors can increase the risk of early puberty (University of Michigan Health System, 2013). This article will review the literature for early and precocious (both central and peripheral) pubertal onset in girls less than 12 years old to achieve a better understanding of potential causes, patient impact, and management options.

The Transactional Model of Stress and Coping, by Lazarus and Folkman (1984), views stress as an interaction between people and their external environment. It interprets stress as a stressor only if the person perceives it as such. However, if perceived as harmless, or even a challenge, then the stress is not viewed as a stressor and may even be viewed as a positive. Additionally, the coping resources the person utilizes can diminish their perception of stress as a stressor. With adequate coping skills, people can change their viewpoints of stressors and actually thrive on life's challenges.

The Transactional Model of Stress and Coping will be examined for girls diagnosed with

early/precocious puberty. This model looks at the diagnosis (early/precocious puberty), the appraisal of the situation (personality factors, social support, coping skills) that interacts with stressors (immunologic/neuroendocrine function), which determine the health outcomes. Within this study, the diagnosis is early/precocious puberty. The appraisal of the situation involves the child's social support network (friends/family), their personality factors (are they anxious children regularly) and their coping skills (how well are they able to cope with breast development, pubic hair growth, physician appointments, treatments, etc.). These factors interact with the endocrinology/pathophysiology of their condition (hyperinsulinemia, hypothyroidism, etc.) to produce a positive health outcome (healthy status, treatment decisions, mood, anxiety/depression/etc.). The goal for the early/precocious puberty child would be having a supportive system, an adaptive personality, and well developed coping skills to achieve a healthy outcome in regards to decision making, mood, and optimal health status (Lazarus & Folkman, 1984).

### **Literature Review**

Research databases Cinhal, PubMed, Sage Premier, as well online journals (Pediatrics) and the American Academy of Pediatrics were searched for journal articles published within the last 15 years. Search terms included early puberty, precocious puberty, early menarche, sexual maturation, and secondary sex characteristics. The search included articles that contained the proposed cause of early/precocious puberty, its impact on girls, and the recommended treatment options.

### **Causes of Early/Precocious Puberty**

**Stress.** Frigon & Trembaly (2005) examined the stress levels of young girls, their family life, and the onset of puberty in relation to behavioral outcomes. They found that the girls who

reported more anxiety at 8 years old had an increased risk of early menses ( $P=0.01$ ).

Consequently, the girls who entered puberty earlier than their peers reported less sleep ( $P=0.002$ ), more externalized problem behaviors ( $P=0.02$ ), and increased difficulty relating to their parents and peers ( $P=0.01$ ).

**Abuse.** Wise, Palmer, Rothman, & Rosenberg (2009) conducted a retrospective of study black women that examined childhood physical/sexual abuse and age of menarche. After adjusted analyses, they found that participants who reported sexual abuse in childhood also reported earlier menarche. Physical abuse had a weak but still statistically significant link with early menarche. Women who reported any childhood abuse were 1.12 times more likely to report early menarche compared to those women who reported no abuse in childhood (95%CI=1.08, 1.16). Physical abuse only victims were 1.05 times more likely to report early menarche (95%CI=1.01, 1.09). Sexual abuse only victims were 1.27 times more likely (95%CI=1.20, 1.35) and physical and sexual abuse victims were 1.22 more likely (95%CI=1.16, 1.28) to report early menarche. Additionally, the more childhood incidences of abuse reported further increased the risk of early menarche: number of sexual abuse incidents of one to three (1.26, 95%CI=1.18, 1.34) and four or more (1.34, 95%CI=1.23, 1.45).

**Obesity.** Davison, Susman, & Birch (2003) conducted a longitudinal study of 183 white girls ranging from 5 to 9 years old to determine if a causal relationship existed between weight status and pubertal timing. Their results indicated that girls at 5 years of age who had a higher percent body fat ( $p<0.01$ ), and girls who were 7 years old with either a higher percent body fat, a higher BMI, or a larger waist circumference were more at risk of undergoing earlier sexual development at 9 years old ( $p<0.001$ ). Approximately 59% of overweight girls at 9 years old showed early pubertal development. Additionally, girls with earlier puberty exhibited higher

estradiol levels. This study may indicate that weight status precedes puberty.

Boynton-Jarrett et al. (2011) studied 32,218 mother-daughter dyads, looking at the correlation between gestational weight gain (GWG) and daughter's age at menarche. They showed that mothers who reported a GWG of <10 lbs. or >40 lbs. were 30% more likely to have daughters with early onset menarche based on adjusted logistic regression models ( $P=0.0059$ ). Additionally, GWG by the mother could influence the fetus' metabolism resulting in increased risk of childhood obesity and hyperinsulinemia, which might affect pubertal onset.

Anderson, Dallal, & Must (2003) compared data from two national surveys conducted 25 years apart to examine the possible relationship between weight and race's possible impact on the average age of menarche. They found that the average age of menarche dropped by approximately 2 ½ months, from 12.75 to 12.54 years, and the percentage of girls aged 10 to 15 years old whose BMI was above the 95<sup>th</sup> percentile increased from 16% to 27% ( $p<.0001$ ). The findings seem to indicate that a higher relative weight is inversely correlated with an onset of early menarche, after controlling for age and race.

Rosenfield, Lipton, & Drum (2009) took the data from the NHANES III (1988-1994) for children aged 8 through 18 years of age. Data was taken from the NHANES III survey of the US population from 1988 to 1994 of children aged 8 through 18 years old. Pubertal stages were estimated at 5%, 50%, and 95% of attainment. They found that girls with excessive BMI showed significantly higher breast appearance prevalence from ages 8.0 to 9.6 years (OR: 3.86 and 2.02, respectively) and pubarche from ages 8.0 through 10.2 years old (OR: 4.50 and 1.87, respectively) than the control group.

**Environmental Toxins.** Environmental toxins are thought to be factors in the development of early/precocious puberty. The Federal Drug Administration (FDA) currently

allows the use of six hormones in the food supply including many sex hormones: estradiol, estriol, testosterone, and progesterone. Estrogen storage in fat tissue increases the risk of overweight children. Additionally, parabens, a known toxin, are found in everyday household items including soap, cosmetics, cleaning products, etc. The xenoestrogens mimic estrogen in the body (Landa, 2012).

Buttke, Sircar, & Martin (2012) studied the association between the exposure of endocrine-disrupting hormones (EDC) and the age of menarche for girls aged 12 to 16 years old. They found that 2,5-dichlorophenol (2,5-DCP) alone and in combination with 2,4-dichlorophenol (2,4 DCP) act as potential EDC's and were inversely associated with an earlier age of menarche (hazard ratios of 1.10; 95% CI: 1.01, 1.10 and 1.09; 95% CI 1.01, 1.19, respectively;  $P=0.025$ ). The phenol 2,5-DCP is a fumigant that is found in common household items such as mothballs, insect repellants, deodorizers, and toilet disinfectants.

Boas et al. (2010) looked at urinary concentrations of twelve phthalate metabolites in relation to serum levels of TSH, thyroid hormones, and IGF-1 in children ages 4 through 9 years old. All associations in girls between peripheral thyroid hormones and unadjusted phthalate metabolites were negative, reaching significance for total T3 with most phthalate metabolites, for free T3 with MEP (monoethyl phthalate) and DEHP, di (2-ethylhexyl) metabolites, and for total T4 with MEP ( $B=-5.19$ ,  $p=0.013$ ) and total phthalate score ( $B=-0.48$ ,  $p=0.037$ ). IGFBP-3 showed a significantly negative association with DEHP and MCIOP (monooxoisobonyl phthalate) metabolites ( $p<0.05$ ). The results seem to indicate negative associations between urinary phthalate concentrations and thyroid hormones, IGF-I (insulin-like growth factor I), and growth in children.

Lopez-Espinosa, Mondal, Armstrong, Bloom, & Fletcher (2012) looked at the

relationship between thyroid function and Perfluoroalkyl acids in children who lived in close proximity to a chemical plant (Teflon) and consumed contaminated drinking water.

Perfluoroalkyl acids (PFAAs), including perfluorooctanoate (PFOA, also called C8), perfluorooctane sulfonate (PFOS), and perfluorononanoic acid (PFNA) were examined by serum concentrations from 2005 through 2006 in 10, 725 children ages 1-17 years of age. The results seem to indicate that serum measurements of PFOA concentrations are associated with thyroid disease (usually hypothyroidism); odds ratio for hypothyroidism was 1.54 [95% confidence interval (CI): 1.00, 2.37] and interquartile range (IQR) contrast of 13 to 68 ng/mL.

In a study of lab mice, Markay, Luque, Munoz de Toro, Sonnenschein, & Soto (2001) examined the relationship between in utero exposure to low doses of bisphenol A (BPA) at 25 and 250  $\mu\text{g}/\text{kg}$ . Their mammary glands were assessed for signs of breast enlargement at 10 days, 1 month, and 6 months of age. At 6 months of age the results of ductal and alveolar structures were significantly higher in both classes of BPA exposed mice compared to the control group. The mammary glands exhibited a 29% ( $P<0.01$ ) and a 25% ( $P<0.05$ ) breast enlargement in the ductal area; a 237% ( $P<0.05$ ) and a 219% ( $P<0.05$ ) increase in the terminal duct area; a 192% ( $P<0.05$ ) and a 139% increase in the terminal end buds; and a 288% ( $P<0.01$ ) and a 361% ( $P<0.01$ ) increase in the alveolar buds area. The results from this study seem to indicate that lower than currently considered significant doses of BPA may lead to early breast enlargement, usually the first sign of puberty.

**Nutrition.** Talpade (2008) looked at the relationship between nutritional intake and body imaging on sexual maturation differences between 7 and 10 year old Hispanic American (HA) and African American (AA) girls. The results indicated that AA girls with secondary sexual characteristics consumed a diet higher in lipids ( $p=.025$ ) and saturated fats ( $p=.048$ ).

Additionally, food consumption and race between the girls who experienced early sexual maturation (one minimum characteristic) found significant differences between the consumption of lipids ( $p=.04$ ) being higher among AA and calcium ( $p=.04$ ) being higher among HA. Higher intakes of calcium among HA girls ( $p=.006$ ) and lipids among AA girls ( $p=.049$ ) showed significant associations with increased breast development.

**Vitamin Deficiency.** Villamor, Martin, & Mora-Plazas (2011) followed 242 girls whose mean age was  $8.8 \pm 1.6$  years for 2.5 years and studied their Vitamin D nutrition in relation to the timing of menarche. The results indicated that Vitamin D-deficient girls were 3.03 times more likely to reach menarche earlier than vitamin D-sufficient girls (95% CI: 1.58-5.83). After adjustments for age at baseline for BMI-for-age z-score (HR: 2.05, 95% CI: 1.03-4.07), the relationship was partially attenuated.

### **Impact of Early/Precocious Puberty**

**Endocrine.** Midyett, Moore, & Jacobson (2003) studied precocious puberty in girls before age 8 years. Within the group, 12.3% of the patients ranging in age from 6 to 8 had pathologic processes related to their precocious puberty, such as insulin resistance/hyperinsulinemia, hypothyroidism, growth hormone deficiency, and congenital adrenal hyperplasia. Approximately 45% of the study population was obese and 81% had additional endocrine pathologies. Girls who exhibited two signs of puberty had the greatest percentage of obesity compared to those with only one sign of puberty ( $P=.024$ ); more than two thirds of the girls who presented with two or more signs of puberty displayed a bone age  $>3SD$  above the mean, indicating a risk for decreased final adult height. Girls with breast development as the only sign of puberty exhibited the same amount of risk to losing adult height as the girls who presented with two signs of puberty. The results seem to indicate that girls under 8 years of

age who present with two signs of precocious puberty should receive a referral to an endocrinologist and those with one sign of puberty should receive, at a minimum, a bone age assessment.

**Cardiovascular.** Güven, Cinaz, & Bideci (2005) examined the relationship between premature adrenarche (PA) and arterogenesis (arterogenic index, AI) in girls (ages 5.4 to 8.6 years old) with premature adrenarche. The bone age with PA positively correlated with AI ( $P < 0.05$ ). Higher bone ages ( $P < 0.05$ ), weight, body mass index (BMI), systolic, diastolic, and mean arterial blood pressures (MBP) were found in the girls with premature adrenarche compared to their age matched counterparts. Additionally, the mean total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), very low-density lipoprotein-cholesterol (VLDL-C), TC/high-density lipoprotein-cholesterol ( $P = 0.011$ ) and LDL-C/HDL-C ratio ( $P < 0.05$ ), and arterogenic index ( $P < 0.05$ ) were significantly higher in the premature adrenarche group. The results seem to indicate a correlation between premature adrenarche and increased cholesterol levels.

**Psychological.** Precocious puberty can have profound effects on an adolescent's psychological well-being. Liao, Missenden, Hallam, & Conway (2005) conducted a retrospective qualitative study of women ages 31 to 65 years who underwent puberty before the age of 7 years old and found two recurring themes: "on being different" (sub themed into "feeling different", "feeling a freak", and "remaining different") and "the adult child" (sub themed into loss of childhood, blurring of boundaries between adult/child, and the sexual child). The adults reported feeling different based on how people treated them. They reported feeling like freaks because providers did not know how to stop their pubertal progression. They felt they remained different even when their peers started puberty because they knew they had started it earlier. On being the

adult child, the adults felt like they were treated like adults while they still retained the cognitive abilities of a child, thereby being robbed of a childhood. The blurring of adult/child boundaries was felt because "...other children are getting cuddled and talked about, and you feel like you're not because you look older, but you're not, you're really young, the same as them." The sexual child was described by one participant who recalled her mother had decided she had breast development due to fondling herself; whereas another participant was told by doctors that her early development was due to sexual abuse (there was none) which decreased her willingness to talk to health professionals

Deardorff, Gonzales, Christopher, Roosa, & Millsap (2005) conducted a retrospective study of women ages 18 to 22 years who were from four major ethnic groups (non-Hispanic white, black, Latino, and Native American) and who experienced a pregnancy in their teens or early 20s. The study examined the relationship between the participant's onset of first menarche, first sexual encounter, first alcohol use, and the age at first pregnancy. The participants sampled experienced menarche earlier than 11.94 years (with early menarche being defined as before age 12). The earlier age of menarche correlated to earlier age at first alcohol use ( $\beta=.16$ ;  $z=4.63$ ), the age at first alcohol use directly and positively related to age at first sex ( $\beta=.40$ ;  $z=11.14$ ) which had a significant increase of earlier age at first pregnancy ( $\beta=.56$ ;  $z=17.59$ ). A second analysis showed that all paths were significant (at  $P<.001$ ) for the following: menarche to alcohol use ( $\beta=.13$ ;  $z=3.79$ ); menarche to sex ( $\beta=.20$ ;  $z=6.02$ ); alcohol use to sex ( $\beta=.33$ ;  $z=10.09$ ); sex to pregnancy ( $\beta=.46$ ;  $z=14.46$ ). The results seem to indicate that early menarche has a direct correlation on early first sexual encounter, early alcohol use, and an increased risk of early pregnancy.

Copeland, Shanahan, Miller, Costello, Angold, & Maughan (2010) studied the outcomes

of early puberty in females. The longitudinal study consisted of girls ages 9, 11, and 13 years old followed into adulthood. Their results showed that participants who reported early pubertal development also reported increased criminal problems ( $P=0.34$ ), early sexual activities ( $P=0.11$ ), and increased social ( $P=0.04$ ) and psychiatric problems ( $P=0.04$ ) during their adolescent years. The largest areas of concern were in substance abuse and conduct problems (odds ratios  $>3.0$ ). These negative behaviors tapered off in adulthood and the girls reached the same level of negative behaviors as their on-time or late puberty peers.

Deng, Tao, Wan, Hao, Su, & Cao (2011) studied young Chinese women in high school (grades 7, 8, 10, and 11) and college students (freshman and sophomore) who reported early, on-time, and late onset of menarche. The results indicated increased psychopathologic emotional symptoms, behavioral symptoms ( $p=0.000$ ), and social adaptation problems ( $p=0.001$ ) for high school girls who reported early menarche ( $p=0.024$ ). Additionally, the female college students exhibited decreased psychopathology symptoms as follows: emotional symptoms ( $p=0.006$ ), behavioral symptoms ( $p=0.003$ ), and social adaptation problems ( $p=0.000$ ). The results indicated higher frequency of disorders, such as psychopathological, suicide, and self-harming appeared in the high school students who reported earlier menarche.

Kim & Lee (2012) evaluated the patterns of behavior and social competency in 34 girls with precocious puberty. Height, body weight, BMI, and pubertal development were evaluated along with a child behavior questionnaire that was completed by the parents. Weight ( $p<0.001$ ) and BMI ( $p=0.001$ ), social competence ( $p=0.048$ ), externalizing problems ( $p=0.029$ ), total behavior problems ( $p=0.008$ ), thought problems ( $0.010$ ), and attention problems ( $0.047$ ) were significantly higher in the precocious puberty group. The results seem to indicate a correlation between increased weight and early puberty increasing the risk of behavior and social problems.

### **Management Options For Gonadotropin-dependent Precocious Puberty**

Children with precocious puberty have increased estrogen levels, which produce initial early skeletal maturation and early epiphyseal plate closure that results in a decreased final adult height. Affected children will have an increased height in early childhood sooner than their on time/late puberty counterparts but will also stop skeletal maturation sooner. Oerter, Manasco, Barnes, Jones, Hill, & Cutler (1991) conducted a study of children diagnosed with precocious puberty who were medicated with deslorelin, a long-acting luteinizing hormone-releasing hormone (LHRH) agonist that was used in LHRH-dependent precocious puberty to examine its effectiveness in increasing final adult height among the participants. The National Institutes of Health initiated the treatment in 1979; the following results are from the first forty-four patients to have attained adult height from the long-term trial. LHRH decreases gonadotropin and sex steroid levels leading to increased final adult height. At the start of treatment, the children were  $7.1 \pm 1.2$  years old, had a mean delay of  $3.1 \pm 0.3$  years between pubertal onset and treatment, and a mean bone age of  $11.8 \pm 1.5$  years. The study group received daily injections of deslorelin for at least  $4.1 \pm 1.3$  years, and had been discontinued from treatment for 2.4 years at the time of study. The final adult height averaged -1.1 SD compared to the normal populations adult height. The final adult height of the participants was significantly greater (-1.1 vs. -2.0 SD,  $P < 0.01$ ) than the pretreatment height, but also significantly less than the predicted height at end of treatment (-1.1 vs. -0.5 SD,  $P < 0.01$ ) and the genetic height derived from the parent's measurements (-1.1 vs. 0.1 SD,  $P < 0.01$ ). The mean adult height for the girls was  $157.0 \pm 5.9$  cm ( $-1.1 \pm 1.0$  SD). The mean proximate adult height was significantly greater than the mean pretreatment predicted height ( $-1.1 \pm 1.3$  SD vs.  $-2.0 \pm 1.3$  SD,  $P < 0.01$ ), by  $5.2 \pm 8.4$  cm for the girls. The most recent predicted height was less than the predicted height at the end of treatment by  $2.2 \pm 4.0$  cm

( $P < 0.01$ ). Proximate adult height inversely correlated with pretreatment bone age ( $r = -0.35$ ,  $P = 0.02$ ). Additionally, basal luteinizing hormone levels ( $P < 0.01$ ), LHRH-stimulated LH levels ( $P < 0.01$ ), LHRH-stimulated FSH levels ( $P < 0.01$ ), and Estradiol levels ( $P < 0.01$ ) all showed decreased serum concentrations at the completion of treatment compared with pretreatment values. The results seem to indicate that while deslorelin decreased hormone levels and increased the pretreatment predicted height in the test subjects by an average of 5 cm, it did not restore them to their full genetic potential.

Kauli, Galatzer, Kornreich, Lazar, Pertzalan, & Laron (1997) studied girls with central precocious puberty (CPP) to determine the benefit of medication therapy on final height (FHt) and target height (THt). Of the total population, 28 were untreated, 26 were treated with cyproterone acetate (CyA), and 48 were treated with GnRH analogue (GnRHA). Their height was compared to their respective target height. The results indicated that girls who received treatment with either medication reached THt above (CyA group: FHt 157.8  $\pm$  5.1, THt 156.8  $\pm$  5.1 cm; GnRHA group: 159.6  $\pm$  6.3, THt 157.7  $\pm$  5.7 cm) their non-treated counterparts (THt  $\pm$  0.5 SD; FHt 160.2  $\pm$  7.1, THt 159.5  $\pm$  6.6 cm).

### **Conclusion**

Early and precocious puberty is an increasingly global problem. Research has been done in many areas showing correlations with overweight/obesity, nutritional/vitamin factors, environmental chemicals/toxins, to name just a few. Identifying the cause of early puberty is essential in preventing adverse psychosocial and health outcomes. Children with early and precocious puberty have an increased risk of short stature, endocrine disorders (diabetes), cardiovascular disease, behavioral problems, sexual abuse, increased alcohol abuse, increased risk of early sexual encounter (which increase risk of STDs and cervical cancer), and increased

risk of teenage pregnancy (increasing risk of low socioeconomic status).

Diagnostic testing should be performed on girls who are less than 8 years old presenting with signs of puberty, or girls between 8 and 10 years old who are exhibiting pubertal development and have any of the following: rapid progression of puberty with a skeletal maturation bone age  $>2SD$  years ahead of their chronological age (diagnosed by x-ray of the wrist) with a predicted height  $>2SD$  (4 inches) below their genetic target height, central nervous system problems (seizures, hydrocephalus, etc.), or behavior problems associated with early physical maturation. Diagnostic testing includes differentiating between central and peripheral puberty. The provider should perform a thorough medical history and physical exam, order blood tests (thyroid profile, Vitamin D levels, hormone levels: LH, FSH, Estradiol), x-ray of hand (to determine bone age), and a GnRH stimulation test with blood sample (with central precocious puberty then the other hormone levels will rise, with peripheral precocious puberty the other hormone levels will remain the same). Tumors can be detected by a CT/MRI of the head and abdomen. Cysts can be detected by ultrasound. If a cause is identified then treating the cause/referral is the preferred method of choice. If bone scans indicate advanced bone age or the child exhibits decreased coping skills with the maturation, referral to a pediatric endocrinologist for further testing and treatment provides advanced care and possible relief of symptoms (Mayo Clinic, 2013).

Treatment of precocious puberty can include treating the underlying disease if any is found, psychological therapy, and medication to delay further pubertal onset. The complications of precocious puberty can include psychological problems, short height, and increased risk of cardiovascular disease (Mayo Clinic, 2013). The goal is to delay the onset of early puberty. This gives the child time to reach psychological maturing, decreases the risk of short height, and helps

decrease the risk of endocrine disorders (diabetes, PCOS) and cardiovascular disease.

With the knowledge gained from research, the healthcare provider can increase his or her screening process by effectively evaluating, diagnosing, and hopefully preventing early or precocious puberty. Modifiable factors include encouraging parents to buy products without parabens, decrease stress in the home, eat a well balanced and nutritious diet, maintain a healthy weight, monitor/decrease risk of sexual abuse, avoid toxins that mimic estrogens, and encourage mothers to maintain a healthy weight during pregnancy to help prevent the risk of early or precocious puberty. Universities, healthcare centers, drug companies, the Federal Drug Administration, and the Environmental Protection Agency need to continue to expand and clarify their research. As early and precocious puberty looks to be a multifactorial problem, additional areas of research need to be completed to understand what else can increase the risk of early pubertal timing. With research findings politicians can then enact statutes and laws to protect young girls from potential hazards in food, household products, etc.

Additional studies need to be conducted to determine more causes of precocious puberty. The earlier a cause is identified the earlier prevention and treatment can be implemented by patients and providers to halt early pubertal timing and decrease its complications. To date, while Canada and other countries have stopped using BPA in their products (a potential endocrine disruptor), thus limiting the American consumers exposure, the FDA has yet to ban it from the US market. The FDA needs to remove BPA and other known toxins from US products.

In conclusion, the American Academy of Pediatrics and other pediatric and medical associations need more concise definitions and parameters implemented. Depending on what article is referenced, the age for early and precocious puberty can be evaluated at less than 6, 8, or 12 years. Also, agencies and physicians debate about the treatment options of precocious

puberty. While some providers may see precocious puberty as a benign condition, others believe the condition warrants further testing to make sure the early onset is not due to an endocrine disorder, tumor, or disease process. More stringent evaluating, diagnosing and managing guidelines from evidenced based practice would allow for better long term outcomes in young girls.

## Matrix

Author & Year	Inclusion Criteria	Type of Study/Treatment	Primary Outcomes /Conclusions
Tremblay & Frigon. (2005). Precocious puberty in adolescent girls: A biomarker of later psychosocial adjustment problems. <i>Child Psychiatry and Human Development</i> , 36(1), 73-94. Doi:10.1007/s10578-00403489-2	Parents of 1039 girls completed a questionnaire about theirs & the family's characteristics. Followed children from 6 years old (non-puberty) until 17 years of age.	Representative sample of 3017 children & their parents. Followed longitudinally from 1986 (children 6 years old) until they were 17 years old. Completed questionnaire yearly evaluating anxiety, stress and pubertal development. Level 3	The results indicated that girls who reported more anxiety at 8 years old had an increased risk of early menses. Stress was measured two ways the first was the Family Adversity Index, which evaluated socioeconomic status, family structure, and parental occupation, with a distribution range from 0.00 (favorable condition) to 1.00 (higher level of adverse conditions); M=0.23, SD=0.23, and M=0.24, SD=0.24 at 6 and 8 years old, respectively). Next, the Stressful Event Checklist, which attributed a 1-point score with a 0 to 5 distribution range for divorce, separation, and disease of the child within the last 12 months that was assessed between 6 and 7 and between 7 and 8 years old; M=0.51, SD=0.84). Consequently, the girls who entered puberty earlier than their peers reported less sleep, more externalized problem behaviors, and increased difficulty relating to their parents and peers.
Davison, Susman, & Birch. (2003). Percent body fat at age 5 predicts earlier pubertal development among girls at age 9. <i>Pediatrics</i> , 111(4), 815-821.	181 girls age 5, 7, & 9 years old with puberty being assessed at 9 years.	Longitudinal correlational study examining relationship between nutrition, weight, BMI, and waist measurement on pubertal timing. Level 4	Girls at 5 years of age who had a higher percent body fat; and girls who were 7 years old with a higher percent body fat, greater linear increase in percent body fat (OR=1.17; 95% CI=1.05-1.30), higher percentile BMI, larger waist circumference, or greater linear increase in weight circumference (OR=1.12; 95% CI=1.01-1.24) were more at risk of undergoing earlier sexual development at 9 years. The girls with earlier puberty exhibited higher estradiol levels.

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Boynton-Jarrett, Rich-Edwards, Fredman, Hilbert, Michels, Forman, & Wright. (2011). Gestational weight gain and daughter's age at menarche. <i>Journal of Women's Health</i> , 20(8), 1193-1200. Doi:10.1089/jwh.2010.2517	32,218 mother/daughter dyads	Prospective cohort study of mother/daughter dyads looking @ mothers gestational weight gain & daughter's age of menarche. Level 4	Mothers who had a Gestational Weight Gain (GWG) of <10 lbs. or >40 lbs. were 30% more likely to have daughters with early onset menarche based on an adjusted logistic regression models (OR=1.31, 95% CI=1.05-1.62, and OR=1.27, 95% CI=1.06-1.56; P=0.0059).
Anderson, Dallal, & Must. (2003). Relative weight and race influence average age at menarche: Results from two nationally representative surveys of US girls studied 25 years apart. <i>Pediatrics</i> , 111(4), 844-850.	1109 girls ages 10+ years and 2218 girls ages 12-15 years old.	National Health Examination Surveys cycles II & III (1963-1970) compared with results from Third National Health and Nutrition Examination Survey (1988-1994) evaluating weight, BMI and age of menarche. Systematic review of correlational studies. Level 4	The results indicated that the average age of menarche dropped approximately 2 ½ months on average, from 12.75 to 12.54 years (NHES 95% CI: 12.69-12.82 years compared to NHANES III 95% CI: 12.44-12.64 years), and the percentage of girls aged 10 to 15 years old were above the 95 <sup>th</sup> percentile for BMI increased from 16% to 27% (BMI z-score 0.93 units higher in NHES and 0.83 units higher; p<.0001 in independent sample <i>t</i> test in NHANES III than girls who had not reached menarche) over the 25 year time period. The higher relative weight was associated with the increased onset of early menarche, after controlling for age and race.
Rosenfield, Lipton, & Drum. (2009). Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. <i>Pediatrics</i> , 123(1), 84-88. Doi:10.1542/peds.2008-0146	Children from the Third National Health and Nutrition Examination Survey and the NHANES III survey of the US population from 1988 to 1994 of children aged 8- through 18 years old. The data was extrapolated from girls with a normal BMI (control group) and those with excessive BMI ( $\geq$ 85 <sup>th</sup> percentile). Pubertal stages were estimated at 5%, 50%, and 95% of attainment.	Survey Sampling Design. Single observational study evaluating the relationship between BMI and pubertal development. Level 4	The results concluded that girls with excessive BMI showed significantly higher breast appearance prevalence from ages 8.0 to 9.6 years (OR: 3.86 and 2.02, respectively) and pubarche from ages 8.0 through 10.2 years old (OR: 4.50 and 1.87, respectively) than the control group

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Buttke, Sircar, & Martin. (2012). Exposures to endocrine-disrupting chemicals and age of menarche in adolescent girls in NHANES (2003-2008). <i>Environmental Health Perspectives</i> , 120(11), 1613-1618.	440 females age 12-16 years old	(NHANES) Cross-sectional, multistage, stratified, cluster sampling survey conducted by the CDC looking at the relationship between potential EDC's and menarche in females. Level 2	2,5-DCP, a potential EDC, was inversely associated with the age of menarche in females (hazard ratios 1.10; CI 95%=1.01, 1.19, P=0.025). This is a fumigant that is also found in mothballs, insect repellants, deodorizers, and toilet disinfectants.
Boas, Frederiksen, Feldt-Rasmussen, Skakkebaek, Hegedüs, Hilsted, Juul, & Main. (2010). Childhood exposure to phthalates: Associations with thyroid function, insulin-like growth factor I, and growth. <i>Environmental Health Perspectives</i> , 118(10), 1458-1464. Doi:10.1289.ehp.0901331	845 children 4-9 years of age. Urinary concentrations of 12 phthalate metabolites & serum levels of TSH, thyroid hormones, & IGF-I. Exclusions were children who suffered from diseases prone to affect growth or endocrine status as well as children with clinical signs of puberty.	Children who had previously participated in a longitudinal cohort study, for which their mothers (1,953) during pregnancy were consecutively enrolled. Study looked at urine phthalate concentrations and the hormone levels in children. Cohort study. Level 4	The results indicated negative associations between urinary phthalate concentrations and thyroid hormones, IGF-1, and growth in children. All association in girls between peripheral thyroid hormones and unadjusted phthalate metabolites were negative, reaching significance for total T3 with most phthalate metabolites, for free T3 with MEP and DEHP metabolites, and for total T4 with MEP (B=-5.19, p=0.013) and total phthalate score (B=-0.48, p=0.037). IGFBP-3 was significantly negatively associated with DEHP metabolites and MCIOP (p<0.05).
Lopez-Espinosa, Mondal, Armstrong, Bloom, & Fletcher. (2012). Thyroid function and perfluoroalkyl acids in children living near a chemical plant. <i>Environmental Health Perspectives</i> , 120(7), 1036-1041.	10,725 children between 1-17 years old that lived near Teflon chemical plant and had consumed local water for at least one year before 2004	Convenience sampling of the population that met the inclusion criteria. Looked at the relationship between PFOA's and thyroid disease. Level 4	The study found that serum measurements of PFOA concentrations were positively associated with thyroid disease (usually hypothyroidism); odds ratio for hypothyroidism (n=39) was 1.54 [95% confidence interval (CI): 1.00, 2.37] for and interquartile range (IQR) contrast of 13 to 68 ng/mL

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Markey, Luque, Munoz de Toro, Sonnenschein, & Soto. (2001). In utero exposure to bisphenol A alters the development and tissue organization of the mouse mammary gland. <i>Biology of Reproduction</i> , 65(2001), 1215-1223.	Sexually mature, female CD-1 mice (8 weeks of age).	Clinical trial with control group. Single nonrandomized trial. Lab mice exposed to BPA in utero and then evaluated at different intervals for breast enlargement after birth. Level 2	The researchers examined the relationship between in utero exposure to low doses of bisphenol A (BPA) at 25 and 250 µg/kg of body and the amount of breast enlargement were assessed at 10 days, 1 month, and 6 months of age. At 6 months of age the results of ductal and alveolar structures related to the control group were significant in both classes of BPA exposure. The mammary glands exhibited a 29% (P<0.01) and a 25% (P<0.05) increase, respectively, in the ductal area; a 237% (P<0.05) and a 219% (P<0.05) increase in the terminal duct area; a 192% (P<0.05) and a 139% increase, respectively, in the terminal end buds; and a 288% (P<0.01) and a 361% (P<0.01) increase, respectively, in the alveolar buds area. Researchers considered the results significant at P<0.05. Even at lower than significant doses of BPA can lead to early breast enlargement, which can also increase the risk of breast cancer throughout a females life.
Talpade, M. (2008). Hispanic versus African American girls: Body image, nutrition, and puberty. <i>Adolescence</i> , 43(169), 119-127.	23 Hispanic Americans & 44 African American girls ages 7-10 years in pre-pubertal & early pubertal stages	Pilot study. Convenience sample. The study looked at the relationship between nutrition and Hispanic and African American girl's pubertal timing. Level 4	The results indicated that AA girls with secondary sexual characteristics consumed higher intakes of Lipids, $\chi^2(3, N=54)=9.337, p=.025$ and saturated fats $\chi^2(3, N=54)=7.918, p=.048$ ; additionally, the Mann-Whitney U test looked at food consumption and race between the girls who experienced early sexual maturation and found the consumption of lipids U (n=28)=36, p=.04; and calcium, U (n=28)=36, p=.04; among HA (n=7) versus AA girls (n=21) who presented with the presence of one sexual secondary characteristic. Finally, there was a significantly high intake of calcium among HA girls that associated with breast development, Mann Whitney U=12, n=6, p=.006 Mean Rank=18 for HA and Mean Rank=9) and a high intake of Lipids among AA girls, Mann Whitney U=21, n=16, p=.049 (Mean Rank=1 for HA and Mean Rank=13).
Villamor, E., Martin, C., & Mora-Plazas, M. (2011). Vitamin d deficiency and age at menarche: A prospective study. <i>American Journal of Clinical Nutrition</i> , 94:1020-1025.	242 girls from the Bogota School Children Cohort. Ages ranged from 8.8 to +/- 1.6 years	Prospective Study. Cohort. The study examined the relationship between Vitamin-D deficient and Vitamin-D sufficient girl's and the timing of pubertal development. Level 4	Vitamin D-deficient girls were 3.03 (95% CI: 1.58-5.83) times more likely to reach menarche than vitamin D-sufficient girls. After adjustments for age at baseline for BMI-for-age z-score (HR: 2.05, 95%CI: 1.03-4.07) revealed attenuated results.

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Midyett, J., Moore, W., & Jacobson, J. (2003). Are pubertal changes in girls before age 8 benign? <i>Pediatrics</i> , 111(1), 47-51.	1,570 girls referred for precocious puberty s/sx	Retrospective chart review by a Pediatric Endocrinology clinic looking at girls referred for precocious puberty signs and their exam findings. Level 4	Girls with two signs of puberty (thelarche, pubarche, or menarche) had greater obesity than those with one sign ( $p=0.24$ ) & displayed a bone age $>3SD$ above the mean. Girls with only breast development had the same risk to lose adult height as those with 2 signs of puberty.
Kim, E., & Lee, M. (2012). Psychosocial aspects in girls with idiopathic precocious puberty. <i>Psychiatric Investigation</i> , 9(1), 25-28. Doi:10.4306/pi.2012.9.1.25	34 girls diagnosed with idiopathic precocious puberty who were patients in the Department of Pediatrics, Chosun University hospital from June 2010 to August 2010. Compared to 39 first year female students in elementary school in Gwang-san gu with no evidence of pubertal development.	Clinical group comparison study. Convenience sample. Examined the relationship between weight and BMI on pubertal timing as well as the resulting psychosocial problems. Level 4	The results indicated that weight ( $p<0.001$ ) and BMI ( $p=0.001$ ) were significantly higher in the precocious puberty group. Additionally, social competence ( $p=0.048$ ), externalizing problems ( $p=0.029$ ), total behavior problems ( $p=0.008$ ), thought problems (0.010), and attention problems (0.047) were significantly higher in the precocious puberty group. The study shows a correlation between that weight impact puberty, and that early puberty increases behavior problems and social competencies.
Güven, A., Cinaz, P., & Bideci, A. (2005). Is premature adrenarche a risk factor for atherogenesis? <i>Pediatric International</i> , 47:20-25.	24 prepubertal girls (age range, 5.4-8.6 years) with 13 age matched controls (5.7-8.5 years).	Cohort study. Study examined the relationship between Lipid values and premature adrenarche. Level 4	Findings included TC/HDL-C ( $\rho$ , -0.54; $P$ , 0.011) and LDL-C/HDL-C ( $\rho$ , -0.0; $P<0.05$ ) and artherogenic index (AI; $\rho$ , -0.43; $P<0.05$ ). Finally, the bone age with PA positively correlated with AI ( $\rho$ , 0.456; $P<0.05$ ) The findings indicate higher bone age, weight, body mass index (BMI), systolic, diastolic, and mean arterial blood pressure (MBP) in the girls with premature adrenarche. Additionally, the mean total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), very low-density lipoprotein-cholesterol (VLDL-C), TC/high-density lipoprotein-cholesterol (HDL-C) and LDL-C/HDL-C ratio, and artherogenic index were significantly higher in the premature adrenarche group as well.
Liao, L., Missenden, K., Hallam, R., & Conway, G. (2005). Experience of early pubertal development: A preliminary analysis. <i>Journal Of Reproductive and Infant Psychology</i> , 23(3), 219-233. Doi.10.1080/02646830500165804	5 participants ages 31-65 years. Retrospective study. All had experienced pubertal development before 7 years old.	Retrospective Single Qualitative study. Examined the subjective feelings/experiences of women who reported early/precocious puberty. Level 4	2 themes found: "on-being different" & "the adult child"

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Wise, L., Palmer, J., Rothman, E., & Rosenberg, L. (2009). Childhood abuse and early menarche: Findings from the black women's health study. <i>American Journal of Public Health, 99</i> (S2), S460-S466.	35,330 Black women	Prospective cohort study. Regression data. Studied the relationship between sexual/physical abuse and pubertal timing. Level 4	After adjusted analyses, sexual abuse was positively correlated with early menarche, and physical abuse had a weak but statistically significant link with early menarche. Women who reported any abuse had 1.12 times the risk of early menarche compared to those who reported no abuse (95%CI=1.08, 1.16). Physical abuse only were 1.05 times more likely for early menarche (95%CI=1.01, 1.09), and 1.27 for sexual abuse only (95%CI=1.20, 1.35), and 1.22 for physical and sexual abuse (95%CI=1.16, 1.28). Additionally, the increased number of sexual abuse incidents of 1 to 3 (1.26, 95%CI=1.18, 1.34) and 4 or more (1.34, 95%CI=1.23, 1.45) increased the risk of early menarche
Deardorff, J., Gonzales, N., Christopher, F., Roosa, M., & Millsap, R. (2005). Early puberty and adolescent pregnancy: The influence of alcohol use. <i>Pediatrics, 116</i> (6), 1451-1456. Doi:10.1542/peds.2005-0542	666 women ages 18 to 22 years who were either African American (N=92), non-Hispanic white (N=191), Latino (N=209), or Native American (159). Recruited at health clinics, shelters, colleges, & private providers).	Convenience sampling of women who were in the target age range & had experienced a pregnancy in their teens or early 20's. Examined the relationship between early pubertal timing and alcohol abuse, first sexual encounters, and pregnancy. Level 4	Experienced menarche lower than 11.94 years (with early menarche being defined as before age 12). Age at menarche related to both age at first alcohol use ( $\beta=.16$ ; $z=4.63$ ). Age at first alcohol use directly and positively related to age at first sex ( $\beta=.40$ ; $z=11.14$ ), which had a significant path to age at first pregnancy ( $\beta=.56$ ; $z=17.59$ ) were also significant. The squared multiple correlation for age at first pregnancy ( $z=5.87$ ) was .32, an indicator of the indirect effect between menarche and pregnancy (6.62). A second analysis showed that all paths were significant (at $P<.001$ ) for the following: menarche to alcohol use ( $\beta=.13$ ; $z=3.79$ ); menarche to sex ( $\beta=.20$ ; $z=6.02$ ); alcohol use to sex ( $\beta=.33$ ; $z=10.09$ ); sex to pregnancy ( $\beta=.46$ ; $z=14.46$ ).
Copeland, W., Shanahan, L., Miller, B., Costello, J., Angold, A., & Maughan, B. (2010). Outcomes of early pubertal timing in young women: A prospective population-based study. <i>The American Journal of Psychiatry, 167</i> :1218-1225. Doi:10.1176/appi.ajp.2010.09081190	1,420 children ages 9, 11, & 13 followed into adulthood	Longitudinal study with 3 cohorts: ages 9, 11, & 13. Examined the relationship between early puberty and behavioral problems. Level 4	Early puberty resulted in criminal problems ( $P=0.34$ ); early sexual activities ( $P=0.11$ ), social problems ( $P=0.04$ ); and psychiatric problems ( $P=0.04$ ) during the adolescent years. The biggest areas of concern were in substance abuse and conduct problems (odds ratios $>3.0$ ). Negative behaviors tapered off in adulthood and the girls reached the same level of negative behaviors as their on-time or late puberty mature peers.

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<p>Deng, F., Tao, F., Wan, Y., Hao, J., Su, P., &amp; Cao, Y. (2011). Early menarche and psychopathological symptoms in young Chinese women. <i>Journal of Women's Health, 20</i>(2), 207-213. Doi:10.1089/jwh.2010.2102</p>	<p>5,597 high school students (grades 7, 8, &amp; 11) &amp; 2,768 college students (freshman &amp; sophomore).</p>	<p>Stratified cluster sampling. Cohort study. Examined the relationship between early pubertal timing and psychopathological symptoms. Level 4</p>	<p>The MSQA indicated psychopathology in emotional symptoms were 20.6%, 15.7%, and 16.9%, respectively, for the early, on-time, and late menarche groups (<math>p=0.024</math>); the percentages in behavioral symptoms were 27.7%, 19.3%, and 19.3%, respectively (<math>p=0.000</math>); the percentages in social adaptation problems were 18.2%, 12.0%, and 12.7% respectively (<math>p=0.001</math>). For college students, the percentages of psychopathology in emotional symptoms were 17.3%, 9.4%, and 12.5%, respectively, for the early, on-time, and late menarche groups (<math>p=0.006</math>); the percentages in behavioral symptoms were 18.2%, 9.8%, and 13.3%, respectively (<math>p=0.003</math>); the percentage in social adaptation problems were 17.3%, 6.8%, and 7.0%, respectively (<math>p=0.000</math>).</p>
<p>Oerter, K., Manasco, P., Barnes, K., Jones, J., Hill, S., &amp; Cutler, G. (1991). Adult height in precocious puberty after long-term treatment with deslorelin. <i>Journal of Clinical Endocrinology and Metabolism, 73</i>(6), 1235-1240.</p>	<p>44 children (38 girls and 6 boys) out of 161 who were the first to reach adult height in a long-term trial of deslorelin. Diagnosis of (Luteinizing hormone-releasing hormone) LNRH-dependent precocious puberty (as determined by response to LNRH)</p>	<p>Longitudinal clinical trial study. Single non-randomized trial. Examined the relationship between early/precocious children's predicted height and their final height after taking Deslorelin. Level 2</p>	<p>At the start of treatment, the children had a mean bone age of <math>11.8 \pm 1.5</math> years prior to starting treatment. The mean adult height for the girls was <math>157.0 \pm 5.9</math> cm (<math>-1.1 \pm 1.0</math> SD). The mean proximate adult height was significantly greater than the mean pretreatment predicted height (<math>-1.1 \pm 1.3</math> SD vs. <math>-2.0 \pm 1.3</math> SD, <math>P&lt;0.01</math>), by <math>5.2 \pm 8.4</math> cm for the girls. The most recent predicted height was less than the predicted height at the end of treatment by <math>2.2 \pm 4.0</math> cm (<math>P&lt;0.01</math>). Proximate adult height inversely correlated with pretreatment bone age (<math>r=-0.35</math>, <math>P=0.02</math>). Basal luteinizing hormone levels decreased from <math>8.7 \pm 5.0</math> IU/L before the treatment to <math>3.1 \pm 1.5</math> IU/L at the end of treatment (<math>P&lt;0.01</math>). The peak LHRH-stimulated LH levels decreased from <math>76.3 \pm 53.1</math> IU/L before treatment to <math>3.8 \pm 2.3</math> IU/L at the end of treatment (<math>P&lt;0.01</math>). Peak LHRH-stimulated FSH levels decreased from <math>24.8 \pm 16.8</math> IU/L before treatment to <math>3.0 \pm 1.5</math> IU/L at the end of treatment (<math>P&lt;0.01</math>). Estradiol levels in the girls were <math>243.7 \pm 229.0</math> pmol/L before treatment and suppressed to <math>58.7 \pm 18.4</math> pmol/L by the end of the treatment (<math>P&lt;0.01</math>). After discontinuation of the medication, the mean <math>\pm</math> SD growth was <math>5.1 \pm 3.2</math>, (<math>r=0.34</math>, <math>P=0.025</math>) and inversely with bone age (<math>r=-0.53</math>, <math>P=0.0002</math>).</p>

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<p>Kauli, R., Galatzer, A., Kornreich, L., Lazar, L., Pertzalan, A., &amp; Laron, Z. (1997). Final height of girls with central precocious puberty, untreated versus treated with cyproterone acetate or GnRH analogue. A comparative study with re-evaluation of predictions by the Bayley-Pinneau method. <i>Hormone Res</i>, 47(2), 54-61.</p>	<p>102 girls with central precocious puberty.</p>	<p>Cohort study. Of the 102 participants, 26 were treated with Cyproterone Acetate (CyA), 48 were treated with GnRH analogue, and 28 were untreated. Examined the difference in final female height between who were treated with either CyA or GnRH or untreated. Level 2</p>	<p>Their height was compared to the respective target height. Approximately half of the untreated girls had a slow course of puberty and reached THt +/- 0.5 SD (FHt 160.2 +/- 7.1, THt 159.5 +/- 6.6 cm); while the other half had an accelerated course of puberty with a FHt well below THt (FHt 150.8 +/- 4.3, THt, 159.2 +/- 5.9 cm) and most were below the height-SDS of both parents. However, the treated girls (both medications) reached THt above (CyA group: FHt 157.8 +/- 5.1, THt 156.8 +/- 5/1cm; GnRHA group: 159.6 +/- 6.3, THt 157.7 +/- 5.7 cm). The results show that both that final height (FHt) is increased with either treatment (cyproterone or GnRH) regimens. Additionally, the optimal treatment should be started in girls younger than 12 years due to a decreased bone age.</p>

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