

## Precocious Puberty

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Precocious puberty (PP) has traditionally been defined as pubertal changes occurring before age 8 years in girls and 9 years in boys. A secular trend toward earlier puberty has now been confirmed by recent studies in both the United States and Europe. Factors associated with earlier puberty include obesity, endocrine-disrupting chemicals (EDC), and intrauterine growth restriction. In 1997, a study by Herman-Giddens et al found that breast development was present in 15% of African American girls and 5% of white girls at age 7 years, which led to new guidelines published by the Lawson Wilkins Pediatric Endocrine Society (LWPES) proposing that breast development or pubic hair before age 7 years in white girls and age 6 years in African-American girls should be evaluated. More recently, Biro et al reported the onset of breast development at 8.8, 9.3, 9.7, and 9.7 years for African American, Hispanic, white non-Hispanic, and Asian study participants, respectively. The timing of menarche has not been shown to be advancing as quickly as other pubertal changes, with the average age between 12 and 12.5 years, similar to that reported in the 1970s.

In boys, the Pediatric Research in Office Settings Network study recently found the mean age for onset of testicular enlargement, usually the first sign of gonadarche, is 10.14, 9.14, and 10.04 years in non-Hispanic white, African American, and Hispanic boys, respectively. For pubic hair, the mean ages were 11.47, 10.25, and 11.43 years, respectively, for non-Hispanic white, African American, and Hispanic boys.

Lowering the age limit of PP in girls per LWPES guidelines has been estimated to misdiagnose 5% to 10% of girls with PP. Generally, girls with secondary sexual characteristics before 8 years should be monitored carefully. Normal puberty in girls most commonly begins with thelarche (the onset of breast buds), followed in a few months by pubarche (the onset of pubic hair), most often resulting from secretion of adrenal androgens (adrenarche). Gonadarche refers to sex hormone production from the ovary or testis.

The differential diagnosis for PP (Table) includes central precocious puberty (CPP), peripheral precocious puberty (PPP), and normal variants such as premature thelarche (PT) and premature adrenarche (PA). CPP (gonadotropin-dependent) results from early activation of the hypothalamic-pituitary-gonadal axis and is much more common in girls and internationally adopted children. The increased risk for CPP in adopted children may reflect nutritional deprivation early in life, followed by increased adiposity after adoption. CPP is idiopathic in 90% of girls and is more likely to be associated with a pathologic cause in boys. Hypothalamic hamartomas (HH) are congenital, non-neoplastic tumors that include gonadotropin-releasing hormone (GnRH) neurons. HH are more common in boys and often present before 4 years of age. Kisspeptin and its receptor are involved in the neuroendocrine control of GnRH secretion, and recent mutations have been found to cause PP.

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**TABLE. Causes of Precocious Puberty**

<b>Central or True Precocious Puberty (Gonadotropin-dependent)</b>
-Idiopathic
-Central nervous system (CNS) tumors (astrocytoma, optic glioma [neurofibromatosis 1], hypothalamic hamartoma, craniopharyngioma, ependymoma, pineal tumor)
-CNS insults (cerebral palsy, hydrocephalus, CNS irradiation, CNS trauma, CNS infection, CNS granulomatous disease, subarachnoid cyst)
-Tuberous sclerosis, Sturge-Weber
-Due to withdrawal of chronic sex hormone exposure
-Gain-of-function mutations of kisspeptin/kisspeptin receptor
<b>Pseudo or Peripheral Precocious Puberty (Gonadotropin-independent)</b>
-Gonadal (McCune Albright syndrome, familial testotoxicosis [activating mutation of luteinizing hormone receptor], ovarian tumor, ovarian cyst, Leydig cell tumor)
-Adrenal (estrogen-secreting adrenal tumor, congenital virilizing adrenal hyperplasia, adrenal functional adenoma/carcinoma)
-Human chorionic gonadotropin-producing tumors (CNS chorioepithelioma, CNS dysgerminoma, CNS teratoma, choriocarcinoma, hepatoma, teratomas)
-Other (primary hypothyroidism, exogenous estrogen exposure, aromatase excess, exogenous testosterone exposure, Peutz-Jeghers syndrome)
<b>Normal Variant Puberty</b>
-Premature thelarche
-Premature adrenarche

PPP (gonadotropin-independent) can be caused by McCune-Albright syndrome (MAS) or familial male-limited PP, in which sex steroids are produced without regulation. The classic triad of MAS includes café-au-lait macules, fibrous dysplasia, and PPP. MAS can present as recurrent ovarian cysts and irregular vaginal bleeding in a prepubertal girl. Estrogen-secreting tumors of the ovary, most often granulosa cell tumors, or Leydig cell tumors producing testosterone in boys are rare causes of PPP. Human chorionic gonadotropin (hCG)-secreting tumors cause PPP in boys and can be located in organs other than gonads, such as hepatoblastoma in the liver, pineal region, brain, or mediastinum.

Congenital adrenal hyperplasia (CAH) can cause PPP from excess androgen production by the adrenal gland. Interestingly, chronic sex hormone exposure from a GnRH-independent process can cause CPP. This can also occur after withdrawal of the exposure, such as after therapy is started for CAH or MAS.

Exogenous estrogen or testosterone exposure can cause PPP. It is important to ask about possible estrogen exposure, including availability of oral contraceptive pills, estrogen-based creams, phytoestrogens, and EDCs, which may have a link with the secular trend toward earlier puberty. An EDC

is defined as an exogenous agent that interferes with the synthesis or action of natural hormones and includes some pesticides and plasticizers. Plant-derived phytoestrogens share a chemical structure with estrogen and are found in soy, including soy formula. Among the other naturally occurring EDCs with estrogenic activity are lavender oil, tea tree oil, and fennel. There have been multiple case reports of transdermal testosterone products causing virilization in children. Because topical testosterone gels may remain on skin 8 hours after application, there is now a black box warning advising children to avoid contact with application sites.

Variations of normal puberty include PT and premature adrenarche (PA). PT, or isolated breast development, is usually benign, with no evidence of linear growth acceleration, rapid progression of breast development, or advanced skeletal maturation found on bone age radiography. PT is more common in toddler girls but can be present at birth or in older girls and is associated with higher baseline follicle-stimulating hormone (FSH) values. PT does not progress, usually regresses over months, and is not associated with PP or early menarche.

PA results from elevations in adrenal androgens causing pubic or axillary hair growth. Bone age radiographs often show

mildly advanced skeletal maturation, and breast development is absent. Androgen concentrations are in the early pubertal range and are helpful to rule out the unlikely diagnosis of CAH or androgen-secreting adrenal tumor. Ideally, androgens are drawn at 8 AM and include dehydroepiandrosterone sulfate, 17-hydroxyprogesterone, androstenedione, and testosterone. Patients with PA may have increased prepubertal growth velocity, although PA is associated with normal onset of gonadarche and normal final height. PA has been linked to increased cardiometabolic risk factors and risk for polycystic ovarian syndrome in later life.

In a child with PP, history should include age of onset, tempo of pubertal progression, linear growth velocity, and the presence of other secondary sex characteristics, such as acne, body odor, and vaginal bleeding. A family history of PP may point to a familial form such as CAH or familial testotoxicosis. Physical examination should include careful Sexual Maturity Rating determination. Identifying common benign variants of puberty, including PT and PA, is critical. Pathology is more likely with rapid tempo of progression, higher Sexual Maturity Rating, acceleration of linear growth, advanced bone age, and multiple sex characteristics. Boys with CPP usually have enlarged testes, while those with PPP have disproportionately small testes relative to other signs of virilization or even prepubertal testes. Boys with PPP may also present with unilateral testicular enlargement in the case of Leydig cell tumor or adrenal rest tumor (rarely bilateral).

A bone age is often helpful, but prepubertal children who are obese can also show significant bone age advancement. Pelvic ultrasonography is unable to distinguish among different causes of PP but may be helpful when combined with other studies. Pelvic ultrasonography should be performed for girls presenting with isolated vaginal bleeding to look for an ovarian cyst or tumor. A diagnosis of CPP can be made based on a basal luteinizing hormone measuring (LH) value of more than 0.3 mIU/mL (0.3 IU/L) (8 AM if possible) using an ultrasensitive assay. The diagnosis can also be based on a peak LH concentration of greater than 5 mIU/mL (5 U/L) after GnRH or leuprolide stimulation. Other criteria include an LH/FSH ratio of more than 0.66 after GnRH stimulation. Ultrasensitive estradiol and testosterone assessment in girls and boys, respectively, may also be helpful. Depending on clinical signs, thyroid function tests, adrenal androgens, and hCG measurements may be indicated.

Reasons for treating CPP include preserving adult height and responding to psychosocial difficulties with early puberty and menarche. For children developing CPP before age

6 years, the benefit of GnRH for preserving adult height is clear. Children between 6 and 8 years old may benefit if they have rapid or advanced puberty, but most affected children at this age have slowly progressive puberty. PP can affect children's self-esteem by making them feel different from their peer group. Further, having a more mature appearance can increase expectations of behavior and academic performance. Even early normal puberty in girls has been associated with more frequent risk-taking and delinquent behavior, earlier sexual debut, and more sexual partners. Only two studies have examined the effect of treating CPP on psychological outcomes in girls, with variable results.

CPP can be treated with GnRH analogs. Maintaining constant serum concentrations of GnRH overpowers the pulsatility of endogenous GnRH. Options include an intramuscular injection of leuprolide acetate every 4 weeks, depot leuprolide acetate administered intramuscularly every 3 months, and histrelin implant that is changed approximately yearly.

**COMMENT:** Evolution by natural selection does not generally move quickly. A rapid change in human physiology suggests forces other than evolution. The earlier onset of puberty in American and European girls documented over the past few decades is a case in point, and, along with the dramatic rise in the prevalence of obesity, increasing exposure to EDCs is a likely culprit. How dangerous these agents can be to a long-evolved homeostatic balance, especially to the fetus and growing child, is demonstrated by one of the more frightening medical encounters with a potent EDC in the not so distant past.

Beginning in the 1940s and for the following 30 years or so, diethylstilbestrol (DES) was given to several million pregnant women at risk for miscarriage in the mistaken belief that it could prevent fetal loss. Worse than ultimately finding DES to be ineffective at preventing miscarriage, strong epidemiologic evidence established in 1971 that young women exposed to DES in utero were at risk for developing vaginal clear cell adenocarcinoma.

Our children are growing up in a world increasingly inundated with plastics, pesticides, and pharmaceuticals that have the potential to do much worse than advance the onset of puberty. We must be activists in promoting the science that can clarify the risks and guide us to sound public health policy.

– Henry M. Adam, MD  
Editor, *In Brief*

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