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What is Normal Puberty and What is not?

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Abbreviations

DHEA: Dehydroepiandrosterone; DHEA-s: Dehydroepiandrosterone sulfate; FSH: Follicle-Stimulating Hormone; GnRH: Gonadotropin-Releasing Hormone; GH: Growth Hormone; TSH: Thyroid Stimulating Hormone; hCG: human Chorionic Gonadotropin; 17-HP: 17- Hydroxy Progesterone; IGF-1: Insulin-like Growth Factor-1; IGF-BP3: Insulin-like Growth Factor Binding Protein-3; LH: Luteinizing Hormone; MRI: Magnetic Resonance Imaging; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate

Normal Puberty

Puberty is the transition from childhood to adulthood, defined by the appearance of secondary sexual characteristics and the achievement of reproductive capacity [1]. It requires the activities of the gonads (gonadarche) and adrenal glands (adrenarche), (Table 1). Prepubertal (prepubescent) period is termed 'childhood quiescence' or 'juvenile pause'. Puberty is triggered when the hypothalamus augments its pulsatile secretion of the Gonadotropin-Releasing Hormone (GnRH), stimulating the pituitary to secrete the gonadotropin hormones LH (Luteinizing Hormone; luteum=yellow) and FSH (Follicle-Stimulating Hormone). Its first biomarker is the 23-fold increase in LH level (from a prepubertal level of ≤0.3IU/L to a late pubertal level of about 7.0IU/L). LH increments activate the ovaries to secrete estradiol and the testes to secrete testosterone.

In females, the LH surge triggers ovulation and development of the corpus luteum, whereas the surge of FSH promotes the development of oocytes and increases the size of the ovaries. Estradiol secretion from the ovary causes: (1) breast development, (2) growth spurt (from a pre-pubertal rate of 4-7cm/y to a pubertal rate of 8-10cm/y) and (3) skeletal maturity (advancement in bone age). The interval between breast development and menarche (mean±SD) is 2.3±0.1y (range, 0.50 to 5.75y). Median age at menarche is 12.43y (mean, 12.8y; range, 10 to 15y) [2]. Most adolescents (62%) menstruate in Sexual Maturity Rating (SMR)-4, 26% in SMR-3, 11% in SMR-5, and 1% in SMR-2 [3]. Less than 10% of girls menstruate <11 y, and 90% by 13.75 y [4].

In males, LH stimulates Leydig cells (~10% of testicular volume) to produce testosterone, whereas FSH stimulates seminiferous tubules (~90% of testicular volume). Thus, FSH is responsible for the testicular size. The lack of FSH in Klinefelter syndrome (47, XXY) causes small testes ('seminiferous tubule dysgenesis'). Testosterone causes virilization (testicular and penile enlargements). Prepubertal testes are 1-3cm^3 (1-3mL) in volume or <2.5cm in length. Testicular volume can be derived from the width and length: [testicular volume (mL)=testicular width (cm) × testicular length^2 (cm^2) × 0.71]. It can also be estimated using orchidometer. A volume of 4mL is equivalent to 2.5 cm length and corresponds to SMR-2 (start of puberty). The testicular volume in SMR-3 is 10-12mL.

Human Chorionic Gonadotropin (hCG) binds to LH receptors, causing testicular activation in the absence of pulsatile GnRH (see below). Thus, germ cell tumors that produce hCG may present with signs suggesting central precocious puberty in boys. These tumors require measurements of hCG in the serum and spinal fluid and brain Magnetic Resonance Imaging (MRI).

Onset of puberty is greatly influenced by genetic and environmental factors, nutrition (childhood dietary habits), physical activity and exposure to toxins [4]. Percentage of body fat is critical for puberty development; a minimum body fat of 17% is required to initiate menses and 22% to maintain regular menses [5]. Onset of puberty is identified in girls by breast budding (thelarche) and in boys by testicular enlargement.

The weak adrenal androgens (androstenedione, Dehydroepiandrosterone [DHEA], and Dehydroepiandrosterone sulfate [DHEA-s, the storage form]) are responsible for the appearance

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Table 1: Normal puberty

Puberty = gonadarche + adrenarche. Gonadarche = hypothalamus (↑gonadotropin-releasing hormone, GnRH) → pituitary (↑LH [luteinizing hormone] + ↑FSH [follicle-stimulating hormone]) → ovaries (↑estradiol) or testes (↑testosterone). Adrenarche = ↑dehydroepiandrosterone sulfate (DHEAs) → pubic hair + axillary hair + acne + body odor. DHEAs causes penile enlargement. DHEAs has no direct effects on testicular size, height velocity, or breast development.
Puberty starts at 8-13y in girls and 9-14y in boys. Its first sign in boys is testicular enlargement (≥4mL) and in girls breast development. Estradiol is responsible for the breast development, female body habitus and menstruation. Adrenal androgens are responsible for the body odor, pubic hair, facial hair, acne, baldness, seborrhea, and male body habitus. Normal sequence in girls is breast buds, growth spurt (8-12cm/y), and menarche. The sequence in boys is testicular enlargement, penile enlargement, and growth spurt (10-14cm/y).
Linear growth: Prepubescent linear growth is 4-7 cm/y. Following the onset of puberty, boys grow a total of 20-30cm (10-14cm/y) and girls grow a total of 15-25cm (8-12cm/y).
Testicular size: Prepubescent testicular volume is 1-3mL and length <2.5cm. Pubertal testicular volume is ≥4mL.
Menarche: Mean age =12.8y; median age =12.43y.
LH (or hCG) → Leydig cells → ↑testosterone LH → ovaries → ↑estradiol FSH → oocytes or seminiferous tubules → ↑gonadal size Estradiol = ↑linear growth + ↑bone age (skeletal maturation) + ↑breast size Testosterone (virilization) → ↑testicular size + ↑penile size Testosterone + aromatase → ↑estradiol → ↑growth + ↑bone age + ↑breast size.
Thelarche = Estradiol Clitoromegaly = ↑Androgens Testicular enlargement = ↑Testosterone

Table 2: Precocious puberty.

Precocious puberty	True (central) precocious puberty	False (peripheral) precocious puberty
♀ Estrogen effects at <8y ♂ Testosterone effects at <9y ↑Growth + ↑bone age Investigations: LH, FSH, hCG, estradiol, testosterone, 17-hydroxyprogesterone, TSH, GnRH-stimulation test, bone age, pelvic/testicular US, brain MRI	♀ ↑LH/FSH → ↑estradiol → breast development ♂ ↑LH/FSH → ↑testosterone + ↑testicular size (≥4mL) ± abnormal brain MRI. GnRH agonist (leuprolide acetate) suppresses GnRH → ↓LH/FSH	↓LH/FSH ↑Estradiol (♀) or ↑androgens (♂ prepubertal testes) GnRH-stimulated LH <4IU/L Peripheral source of the hormones, such as late-onset congenital adrenal hyperplasia, hCG-secreting tumors, exogenous, and functional ovarian cyst or tumor.
Brain tumors explain ~30% of the male central precocious puberty and <10% of the female central precocious puberty. Laboratory evidence of central precocious puberty includes: (1) LH >0.3IU/L; (2) GnRH-stimulated LH >5-8IU/L; and (3) estradiol >20pg/mL or >73pmol/L (pubertal range).		

of pubic hair (pubarche), axillary hair (1-2y after pubic hair), acne (oily skin), and adult body odor in females and males. Biomarkers of adrenarche include increased DHEA-s from 30µg/dL (=0.81 micromole/L; pre-pubertal) to 150µg/dL (=4.07 micromole/L; post-pubertal). Excess adrenal androgens (e.g., congenital adrenal hyperplasia) causes penile enlargement, but with normal testicular size.

The ovarian and adrenal maturation in girls increases estradiol production, resulting in physiologic leukorrhea (vaginal discharge). The increased estradiol at the onset of puberty causes thickened vaginal epithelium, increased mucoid secretions, and a shift from alkaline to acidic environment. This form of physiologic leucorrhea represents the effects of estradiol in SMR-3; menarche usually begins within 6 mo of the physiologic leucorrhea.

Labial adhesions (vestibule obstruction by a thin membrane) are self-limiting and resolve before puberty. If extensive or symptomatic, topical estrogen (estradiol or conjugated estrogen once or twice daily for 4-6 weeks) or topical steroid (0.05% betamethasone for 4-6wk) could be used.

Estrogens promote lipogenesis and the female physical build of fat distribution. Androgens, on the other hand, are lipolytic and promote muscular development. Thus, the increased BMI (Body Mass Index) in puberty leads to increased body fat in girls and increased lean body mass in boys. Females are at risk of the "athlete triad": (1) disordered eating (e.g., anorexia nervosa), (2) amenorrhea and (3) osteoporosis (↓body fat → delayed puberty → ↓ovarian function → ↓estradiol).

The pubertal peak height velocity of 8-10cm/y is achieved in girls in SMR 2 to 3 (1y before menarche) and in boys at SMR 3 to 4. About 8cm linear growth remains after menarche. Pubertal growth spurt in boys starts 2y later than that in girls. This longer period of prepubertal growth and the greater pubertal height velocity result in an adult height difference of about 13cm between males and females. The increased height velocity in puberty is linked to estradiol (its source in girls is the ovary and in boys the "testosterone + aromatase → estradiol"), causing direct effects on the epiphysis. The increased pulsatile Growth Hormone (GH) also contributes to the rise in height velocity at puberty. Other contributing hormones are thyroxin and cortisol.

Children growing ≤4cm/y need work-up for GH deficiency (Insulin-like Growth Factor-1 [IGF-1] and Insulin-like Growth Factor Binding Protein-3 [IGF-BP3]), hypothyroidism (TSH and free T4) and Cushing disease (↑cortisol due to pituitary tumor secreting Adreno Cortico Tropic Hormone [ACTH]).

Abnormal Puberty

Precocious (premature) puberty signifies the appearance of secondary sexual characteristics before 8y in females or 9y in males, usually due to high sex hormones (estradiol or testosterone). True (central) precocious puberty (gonadotrophin-dependent) is characterized by pubertal LH (>0.3IU/L); whereas peripheral precocious puberty (gonadotropin-independent) is characterized by pre-pubertal LH (<0.3IU/L) [6].

Testicular size is important distinguisher between central and peripheral precocious puberty in boys. In central precocious puberty, the testicular volume is ≥4mL (stimulated by FSH and LH). Typical investigations include LH, FSH, hCG (human Chorionic Gonadotropin), estradiol, testosterone, 17-hydroxyprogesterone

Table 3: Premature thelarche - "Breast development in girls <2y is both common and benign.

• Benign / isolated finding / non-progressive / starts at <2y / normal linear growth / normal bone age / no adrenal puberty (pubic hair) / LH-FSH levels are prepubertal.
• Monitor effects of DHEA-s every 6mo for 2y / no workup is needed.
If necessary, initial investigations include bone age, estradiol, FSH, and LH. Brain MRI and GnRH stimulation test are necessary only if results suggest precocious puberty (advanced bone age).

Table 4: Premature adrenarche - "Prepubertal breasts, testes, and linear growth."

• Early-onset of adult body odor, pubic/ axillary hair, and acne (♀ <8y, ♂ <9y).
• Pathologic causes include late-onset congenital adrenal hyperplasia, obesity, CNS insult, Cuching syndrome, and adrenal tumors.
• Investigations include 17-OH progesterone, androstenedione, DHEA, DHEAS, and testosterone.
• DHEA-s increases from 30 to 150µg/dL (0.81 to 4.07micromol/L); LH, FSH, testosterone, and estradiol remain prepubertal.
• A bone age within 1y of the chronologic age rules out late-onset congenital adrenal hyperplasia.
• ACTH stimulation test and adrenal imaging distinguish an adrenal tumor from late-onset congenital adrenal hyperplasia.

Table 5: Delayed puberty - High LH and FSH signify a failing gonad; whereas low LH and FSH signify a failing pituitary.

• ♀ No breast development by 13y, failure to menstruate by 16y, or >5y to complete puberty.
• ♂ No testicular enlargement by 14y or >5y to complete puberty.
• Investigations: Blood counts, CRP, serum electrolytes, serum creatinine, ALT, free T4, TSH, LH, FSH, pelvic ultrasonography, and bone age.
• Causes: (1) Hypergonadotrophic hypogonadism (Turner, Klinefelter, gonads autoimmune disorder), (2) hypogonadotrophic hypogonadism (Kallmann, Prader Willi syndrome), and (3) others (e.g., malnutrition).
• Treatment may include hormone replacement according to the underlying cause.

(elevated in congenital adrenal hyperplasia), TSH, GnRH stimulation test, bone age, pelvic or testicular ultrasound and brain Magnetic Resonance Imaging (MRI) (Table 2) [6].

True (central) precocious puberty is more benign and more common in girls than in boys. Girls present with breast development and accelerated growth due to an early activation of the pulsatile GnRH secretion, with subsequent LH and FSH signaling and ovarian activity (estradiol production). Boys present with progressive testicular and penile enlargements (gonadarche with or without adrenarche), increased linear growth and advanced bone age.

In contrast to girls in whom it is often idiopathic, in boys central precocious puberty is more often caused by underlying central nervous system pathology (e.g., hypothalamic hamartoma, pineal gland cyst or tumor and optic glioma). Thus, brain MRI is necessary. Brain tumors account for about 30% of the male central precocious puberty and for <10% of the female central precocious puberty [7]. Brain MRI is indicated in all young boys (<9 y) with large testes (≥4 mL).

Results supporting central precocious puberty include: (1) basal LH >0.3IU/L, (2) GnRH-stimulated LH >5-8IU/L (>5IU/L suggestive; >8IU/L diagnostic) and (3) a random estradiol level of >20pg/mL (>73pmol/L, pubertal range) [8].

Central precocious puberty causes early fusion of the epiphyseal growth plates (loss of final height). Treatment with GnRH agonist, such as leuprolide acetate suppresses the pulsatile release of GnRH necessary to stimulate puberty and increases the final adult height by about 10cm until 10-12y of age. Monitoring LH suppression is essential.

Example of central precocious puberty: A 6y old girl develops progressive breast enlargement over six months. During this period, she needed to change her clothing and shoes frequently. She is not taking any medication and there is no one in the family with early puberty. Her height is at the 95th centile (midparental height, MPH, 25th centile) and her linear growth velocity is 8.0cm/y. Her breast is at SMR-3 and pubic hair at SMR-2. Her laboratory results show normal TSH (Thyroid Stimulating Hormone) and free T4. Basal LH was 0.5IU/L (reference: prepubertal ≤0.3IU/L and late-pubertal ≥7.0IU/L) and GnRH-stimulated LH 10IU/L (reference: >5IU/L suggestive and >8IU/L diagnostic of central precocious puberty). Estradiol level was 92pmol/L (25pg/mL; reference: prepubertal <20pg/mL). MRI pituitary was unremarkable. She was considered to have idiopathic central precocious puberty and treated with GnRH agonist.

False (peripheral) precocious puberty may originate from the ovary (e.g., a functional ovarian cyst or tumor), adrenal gland (e.g., late-onset congenital adrenal hyperplasia), exogenous hormone exposure, activating variants in the LH receptor gene (e.g., autonomous testosterone production from the testes) or human Chorionic Gonadotropin (hCG) secreting tumor (e.g., germinoma). hCG is structurally similar to LH; it can stimulate LH receptors on the testes. The testes can be pubertal in volume in tumors secreting hCG. Treatment is directed toward the underlying cause. For example, treating late-onset congenital adrenal hyperplasia with an adequate corticosteroid replacement would inhibit the sexual development and the growth of puberty.

Example of peripheral precocious puberty: A 2.5y old girl develops a breast over one month. This problem is followed by vaginal bleeding that lasted for 5 days. She has no pubic or axillary hair. There is no significant change in her height. She is not taking any medication and there is no family history of an endocrinopathy or early puberty. On examination, her breast is at SMR-3 and pubic hair at SMR-1. Laboratory results show LH 0.3IU/L (reference: prepubertal ≤0.3IU/L), estradiol 99pmol/L (27pg/mL; reference: prepubertal <20pg/mL) and GnRH-stimulated LH 3.0IU/L (reference: >5IU/L suggestive and >8IU/L diagnostic of central precocious puberty). Pelvic ultrasound shows a well-defined echo-free cystic lesion in the left adnexa, measuring 3.5cm x 2.2cm (Figure 1). This finding is confirmed on the pelvic MRI. Over the following two months, her breast regressed and there was no vaginal bleeding. Repeated pelvic ultrasound shows resolution of the ovarian cyst.

Premature thelarche represents an: (1) isolated breast development (2) non-progressive (no change in size over 6mo) and (3) starts at <2y. It is caused by sufficient LH and FSH that stimulate ovarian estradiol production. It is benign and characterized by normal bone age (skeletal maturation) normal linear growth (absence of rapid height acceleration) and lack of adrenal puberty (adrenarche). The sex hormones (LH and FSH) remain prepubertal (GnRH-FSH predominant rather than GnRH-LH). These girls need to be monitored for androgen effects (DHEA-s) every 6mo for 2y, no workup is needed. If necessary, initial investigation may include bone age, estradiol, FSH, and LH. Brain MRI and GnRH stimulation test (assesses LH response to GnRH) are necessary only if initial

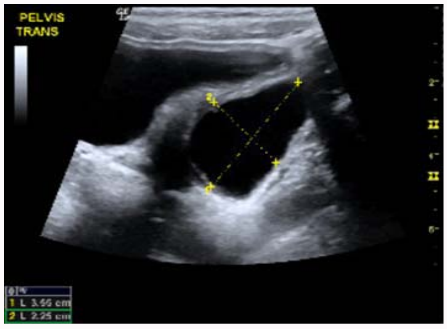

Figure 1:

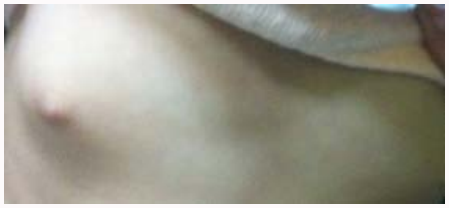

Figure 2:

investigation suggests precocious puberty (e.g., advanced bone age). Because all children 2y go through a period of "mini puberty" when GnRH is not fully inhibited, it is difficult to distinguish premature thelarche from true central precocious puberty in these children based on biochemical testing. Thus LH, FSH and estradiol levels are unnecessary unless there are progressive symptoms or signs of adrenarche. In many cases, there will be a regression of the breast tissue. The breast tissue however may persist or progress to central precocious puberty. In summary development of breast tissue is common in girls <2y and it is usually benign.

Example of premature thelarche: A 30mo old girl has an enlarged breast tissue (SMR-3 with enhancement of breasts and areolae as shown in the (Figure 2)) since 4mo of age. It has not significantly changed in size over the last 2y. Linear growth remains normal. There is no pubic hair.

Premature adrenarche describes the early-onset of adult body odor, pubic hair, axillary hair and acne in <8y old girls or 9y old boys. Characteristically there is no virilization (testicular enlargement), rapid height growth velocity (mainly effects of estradiol) or breast development (ovarian activity, estradiol). The lack of thelarche indicates low estradiol. These young children may have higher DHEA and DHEA-s levels or may be sensitive to low values of these hormones. Follow-up is necessary for 2y. Premature adrenarche may increase the risk of Polycystic Ovarian Syndrome (PCOS) later in adulthood.

Premature adrenarche could be benign or pathologic, associated with late-onset congenital adrenal hyperplasia, obesity, CNS insults, Cuching syndrome or adrenal tumor. A bone age within 1y of the chronologic age rules out late-onset congenital adrenal hyperplasia. Other investigations include 17-OH progesterone, androstenedione, DHEA, DHEAS and testosterone.

In premature adrenarche, DHEA-s increases from 30 to 150µg/dL (0.81micromol/L to 4.07micromol/L), but LH, FSH, testosterone and estradiol remain prepubertal. A radiograph of the left wrist typically reveals normal skeletal maturation (lack of estradiol effects). Adreno

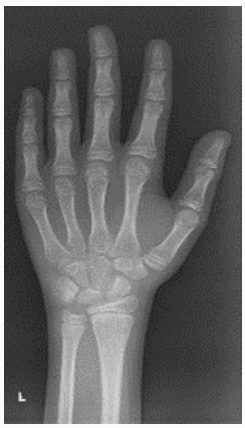

Figure 3:

Cortico Tropic Hormone (ACTH) stimulation test (measures the release of cortisol, aldosterone, DHEA and DHEA-S in response to ACTH) and adrenal imaging distinguish between an adrenal tumor and late-onset congenital adrenal hyperplasia.

Example of premature adrenarche: An 8y old boy has pubic hair since 3 months ago. He has adult body odor and acne on his forehead. He takes no medication and there is no exogenous exposure to androgen. He has no headache or changes in vision. There are no family members with precocious puberty. On examination, he appears older than his age and has a well-defined muscle tone. He has inflammatory acne over his forehead and comedonal acne on his nose. He has prepubertal phallus and sized testes (2mL) which are palpable in the scrotum. His pubic hair is at SMR-3. Linear growth velocity is normal. Serum DHEA-s level is 150µg/dL (4.07micromol/L). Bone age, 17-OH progesterone, androstenedione and testosterone are normal.

Delayed puberty is defined as absence of the initial signs of puberty at an age that is 2.0 to 2.5 standard deviation beyond the population mean. In girls, it is considered when there is no breast development by 13y, failure to menstruate by 16y or >5y between the start of breast development and menarche. In boys, it is considered when there is no testicular enlargement by 14y or >5y to complete puberty [9]. Initial investigations include blood counts, C-Reactive Protein (CRP), serum electrolytes, serum creatinine, ALT (Alanine amino Transferase), free T4, TSH (Thyroid Stimulating Hormone), LH, FSH, karyotype, pelvic ultrasonography (to assure normal anatomy) and bone age. High LH and FSH signify failing gonads and low LH and FSH signify failing pituitary. Causes include: (1) hypergonadotrophic hypogonadism (Turner, Klinefelter, gonads autoimmune disorders), (2) hypogonadotrophic hypogonadism (Kallmann, Prader Willi syndrome) and (3) Other causes, such as malnutrition. Treatment may include short or long-term sex hormone replacement according to the underlying cause.

Example of delayed puberty: A 13y old girl is seen because of the family concern of being short and has no signs of puberty (compared with her older sister when she was at the same age). There was no family history of short stature or delayed puberty. Her weight is at the 10th centile and height is less than the 3rd centile (-3.0 SD). Her breast is at SMR-1 as well as the pubic hair. She has webbed neck. Results of her laboratory investigation show normal TSH, FT4 and IGF-1. She has elevated LH, elevated FSH and low estradiol. Her bone age is 10y (Figure 3). Her chromosomal study reveals 45XO (Turner

syndrome). She is started on growth hormone followed by estradiol supplement.

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