Transition to adulthood: abnormalities of pubertal development and fertility risk in adolescents

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"Soon you will start to notice changes to your body... massive, horrifying changes."
Puberty initiation

**Reactivation of the hypothalamic-pituitary-gonadal axis initiates puberty.**

- **kisspeptin**
  - GnRH pulses during sleep and eventually during waking hours
  - LH \(\rightarrow\) FSH
  - gonadal hormones
  - secondary sexual characteristics and gametogenesis

In both sexes, puberty requires maturation of gonadal function and increased secretion of adrenal androgens.
During fetal, early neonatal and pubertal development, a pulsatile hypothalamic secretion of GnRH stimulates pituitary gonadotropin biosynthesis and secretion that, in turn, stimulates testicular steroid and peptidic hormone production. The dotted line represents spermatogenesis, which occurs only after puberty. Abbreviations: AMH, anti-Müllerian hormone; FSH, follitropin; GnRH, gonadotropin-releasing hormone; hCG, human choriogonadotropin; IB, inhibin B; LH, lutropin; T, testosterone. Bowater et al: Nature Reviews Endocrinology 8, 172-182 (March 2012)
Normal pattern of puberty

Boys: mean onset: 11.8 years (9 - 14 years) - ethnicity!
The first evidence: enlargement of the testes to a volume greater than 4 mL or a length greater than 2.5 cm. It is not until midpuberty, when testosterone levels are rapidly rising, that boys experience voice change, axillary hair, facial hair, and the peak growth spurt. Spermatogenesis is mature at a mean age of 13.3 years.

Girls: mean onset: 10.4 years (8 -13 years ) ethnicity!
The initial pubertal event is typically the appearance of breast buds, although a small percentage of girls will develop pubic hair first. In an even smaller percentage of girls, menstrual cycling may appear first. Initial breast development often occurs asymmetrically and should not be of concern. Breast development is primarily under the control of estrogens secreted by the ovaries, whereas growth of pubic hair and axillary hair results mainly from adrenal androgens. Unlike in boys, the pubertal growth spurt in girls occurs at the onset of puberty. Menarche usually occurs 18 to 24 months after the onset of breast development (mean age: 12.5 years). Although most girls have reached about 97.5% of their maximum height potential at menarche, this can vary considerably. Consequently, age of menarche is not necessarily a good predictor of final adult height.
Pubertal development is measured on the Tanner scale.

- **Prepubertal**
  - Stage I: Germ cells first appear
  - Stage II: Pubic and axillary hair begin to develop
  - Stage III: Breast development begins
  - Stage IV: Pubic hair becomes dense
  - Stage V: Complete development

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Complete development is indicated by Stage V where pubic hair becomes dense and other secondary sexual characteristics are fully developed.
Adrenarche refers to the time during puberty when the adrenal glands increase their production and secretion of adrenal androgens. Plasma concentrations of dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S), the most important adrenal androgens, begin to increase in children by approximately 6 to 8 years. However, the signs of adrenarche, such as pubic hair, axillary hair, acne, and body odor do not typically occur until early puberty to midpuberty. The control of adrenal androgen secretion is not clearly understood, but it appears to be separate from GnRH and the gonadotropins.

- premature adrenarche
In both boys and girls, the pubertal growth spurt is primarily controlled by the gonadal steroid estrogen. In both sexes, gonadal (and adrenal) androgens are aromatized to estrogens. Estrogens augment growth hormone (GH) and insulin-like growth factor I (IGF-I) secretion. Estrogens also suppress osteoclast activity and prolong the life span of osteoblasts and osteocytes. Androgens have a small independent role in maintenance of adequate bone mineral density. At the end of puberty, linear growth is nearly complete as a result of the effects of gonadal steroids on skeletal maturation and epiphyseal fusion.
Sexual precocity

Pubertal signs before 8 years in girls, 9 years in boys
- girls: 6-8 years, slow progression: no intervention
- CNS symptoms! family concerns! speed of progression!

Differential (benign):

Benign premature thelarche is defined as isolated breast development in girls without other signs of puberty such as linear growth acceleration and signs of adrenarche, such as pubic hair, axillary hair, body odor, and acne. <2 years or 6-8 years, GnRH stimulation: predominant FSH response

Benign premature adrenarche, which occurs in both sexes, is defined as the early development of pubic hair with or without axillary hair, body odor, and acne. There are no signs of gonadarche in benign premature adrenarche; girls have no breast development, and boys have no testicular enlargement. DHEA, DHEAS elevated. Rule out CAH (17-OHP) and adrenal tumors!
Central precocious puberty

Precocious puberty, regardless of the cause, is associated with **accelerated linear growth and skeletal maturation** secondary to **elevated sex steroid** levels. Children with precocious puberty are often tall for their age during childhood. However, skeletal maturation may become more advanced than stature, thus leading to **premature fusion of the epiphyseal growth plates and a compromised final adult height**. In addition to the physical consequences of early puberty, social and **psychological aspects** may need to be considered.

Precocious puberty predominantly affects **girls**. The disparity in overall prevalence of precocity is explained by the large numbers of girls with central idiopathic precocity, a condition that is less common in boys. At least 80% of all precocious puberty in girls is central **idiopathic**. The prevalence of organic causes of precocious puberty (CNS lesions, gonadal tumors, and specific underlying diseases) is similar in both sexes.
Diagnosis:

physical examination (Tanner staging, café-au-lait spots, neurologic signs)

history (exposure to exogenous steroids or estrogen receptor agonists (e.g., lavender oil or tea tree oil), onset of pubertal signs and rate of progression, presence or history of CNS abnormalities, and pubertal history of other family members)

Height measurements (plotted on a growth chart, growth pattern, growth velocity)

Bone age

Sex steroid levels (testosterone more accurate than estradiol)

GnRH dependency (GnRH test: LH›FSH)

Treatment:

GnRH depot, im injection once a month
Causes of precocious puberty

• Central (GnRH-Dependent)
  
  Idiopathic true precocious puberty
  CNS tumors (hamartomas, hypothalamic tumors)
  CNS disorders (meningitis, encephalitis, hydrocephalus, trauma, abscesses, cysts, granulomas, radiation therapy)

• Peripheral (GnRH-Independent, suppressed FSH, LH)

Males

  Human chorionic gonadotropin (hCG)-secreting tumors (CNS, liver)
  CAH (21-hydroxylase, 3-beta-hydroxysteroid dehydrogenase, or 11-hydroxylase deficiency)
  Adrenal tumors
  Leydig cell testicular tumors
  Familial gonadotropin-independent Leydig cell maturation (testotoxicosis)
  McCune-Albright syndrome (polyostotic fibrous dysplasia)

Females

  Follicular cysts
  Ovarian tumors
  Adrenal tumors
  CAH (21-hydroxylase, 3-beta-hydroxysteroid dehydrogenase, or 11-hydroxylase deficiency)
  Exogenous estrogen
  McCune-Albright syndrome (polyostotic fibrous dysplasia)
Testotoxicosis

- Male-limited autosomal dominant, gonadotropin-independent form of male precocious puberty.
- True precocity with bilateral testicular and phallic enlargement and growth acceleration by 4 years of age.
- Serum testosterone levels are high, but serum gonadotropins are low, and GnRH testing shows a prepubertal response. By midadolescence to adulthood, GnRH stimulation demonstrates a more typical LH-predominant pubertal response.
- **Activating mutation in the gene encoding the LH receptor.** The mutant LH receptors in the testes are constitutively overactive and do not require LH binding for their activity, but they produce testosterone autonomously. Treatment options are the same as for boys with McCune-Albright syndrome. If central precocious puberty has been induced, GnRH agonists may also be part of the treatment plan.
McCune-Albright syndrome

- triad of GnRH-independent precocious puberty, irregular (coast-of-Maine) café-au-lait lesions, and polyostotic fibrous dysplasia (two of these)
- It can affect both sexes, but it is seen infrequently in boys. In girls, breast development and vaginal bleeding occur with sporadic increases in estradiol from autonomously functioning ovarian cysts.
- Serum gonadotropin levels are low, and GnRH testing elicits a prepubertal response. With time, however, increased estradiol may mature the hypothalamus, thus leading to true central GnRH-dependent precocity. The syndrome can be associated with other endocrine dysfunction including hyperthyroidism, GH excess, and hypercortisolism. In affected tissues, there is an activating mutation in the gene that encodes the alpha-subunit of Gs, the G-protein that stimulates adenylate cyclase. Endocrine cells with this mutation have autonomous hyperfunction and secrete excess amounts of their respective hormones.

Girls with McCune-Albright syndrome are generally treated with a medication that inhibits the aromatization of testosterone to estrogen. Other trials have been performed using tamoxifen, an estrogen receptor antagonist. In boys, treatment consists of either inhibiting androgen production or using a combination of an aromatase inhibitor that blocks the conversion of androgen to estrogen and an antiandrogen that antagonizes the effects of androgens at the receptor.
21-hydroxylase-deficient CAH

- The most common adrenogenital syndrome is 21-hydroxylase deficiency.
- Girls usually develop virilization in utero, resulting in a degree of sexual ambiguity. They are discovered at birth and should be diagnosed within the first few days of life by finding a greatly elevated serum 17-OHP level.
- Boys have normally formed genitalia and therefore are not identified on physical examination at birth.
- In the more common salt-losing form of the disease, boys present with vomiting, shock, and electrolyte disturbances at 7 to 10 days. Fortunately, with neonatal screening for 21-hydroxylase deficiency, boys are being diagnosed before they develop life-threatening electrolyte abnormalities.
- **Late-onset CAH:** boys and girls do not waste salt, late childhood with signs of adrenarche, such as pubic hair, acne, body odor, acceleration of linear growth, and skeletal maturation.
- **Treatment** for all forms of CAH is directed at reducing serum androgen levels by replacing glucocorticoids to reduce pituitary secretion of ACTH. Insufficient glucocorticoid replacement leads to a compromise in final adult height secondary to advanced skeletal maturation, whereas excessive glucocorticoid replacement leads to short stature because of the direct effects of glucocorticoids on bone. Serum markers, growth curves, and bone age radiographs must be carefully monitored. In salt-wasting CAH, the mineralocorticoid fludrocortisone is also required. This is not necessary in the non–salt-wasting forms of CAH.
Hypothyroidism and precocious puberty

Rarely, severe primary hypothyroidism may cause breast development in girls and increased testicular size in boys. The exact mechanism is unclear, but one theory is that thyroid-stimulating hormone (TSH), which is elevated in primary hypothyroidism, can **stimulate the FSH receptor** on the gonads. These children generally present with **growth deceleration** as typically seen in hypothyroidism, rather than growth acceleration as typically seen in precocious puberty. Bone age is usually delayed. Thyroid hormone replacement results in regression of pubertal changes, and no other therapy is necessary.
Adolescent gynecomastia

• Normal boys often have either unilateral or bilateral breast enlargement during puberty. Generally starts during early puberty and resolves within 2 years. The cause of gynecomastia is not clearly understood, but it may be related to an elevated ratio of estradiol to testosterone. Treatment consists primarily of reassurance and support. However, if resolution does not occur or if breast enlargement is excessive, surgery may be warranted. Surgery should be avoided until puberty is complete, to avoid recurrence of gynecomastia.

• Pathologic conditions associated with gynecomastia include Klinefelter syndrome and various other testosterone-deficient states. Tea tree oils and lavender oils have been associated with gynecomastia in boys. Some prescription medications, such as atypical antipsychotics, may cause gynecomastia and galactorrhea. Evidence is mixed regarding the connection of cannabis abuse and gynecomastia.
Delayed puberty

- no pubertal signs by 13 years in girls and by 14 years in boys. An abnormality in the pubertal axis may also manifest as a lack of normal pubertal progression, which is defined as more than 4 years between the first signs of puberty and menarche in girls or more than 5 years for completion of genital growth in boys.

- there is a high incidence of delayed puberty and primary amenorrhea in girls with anorexia nervosa and in girls who are highly competitive athletes. These girls have hypogonadotrophic hypogonadism that appears to be directly related to their low body fat. Girls with a low body mass index (BMI) also have low circulating leptin and estrogen levels and are more likely to have delayed puberty or menstrual dysfunction. There appears to be a minimum leptin level that is permissive for pubertal development. When severely underweight girls improve their BMI, puberty ensues and progresses to menarche appropriately.
Constitutional growth delay is the most common cause of delayed puberty. Children with this growth pattern generally have a fall-off in their linear growth within the first 2 years of life. After this, growth returns to normal, but along a lower growth channel than would be expected for parental heights. Skeletal maturation is also delayed, and the onset of puberty is commensurate with bone age rather than chronologic age. Delay in puberty postpones the pubertal growth spurt and closure of growth plates, so that the child continues to grow after his or her peers have reached their final adult height. A key feature of this growth pattern is normal linear growth after 2 years of age. There is often a family history of “late bloomers.”


Evaluation of delayed puberty

A eunuchoid body habitus is often evident in children with abnormally delayed puberty; a decreased ratio of upper to lower body and a long arm span characterize this habitus. As a rule, serum gonadotropin levels are measured first to determine whether the child has hypogonadotropic hypogonadism (gonadotropin deficiency) or hypergonadotropic hypogonadism (primary gonadal failure). If a child’s bone age is less than the normal age for puberty to start, gonadotropin levels are not a reliable means of making an accurate diagnosis.
Normal or suppressed gonadotropins indicate a failure of the pituitary to stimulate gonadal steroid production. *Chronic illness, malnutrition, excessive exercise, or anorexia* can cause a functional deficiency of gonadotropins that reverses when the underlying condition improves.

- **Hyperprolactinemia** can also manifest as delayed puberty, and only 50% of the time will there be a history of galactorrhea.

- **diabetes mellitus**

- **glucocorticoid excess**

- **hypothyroidism**

- Pituitary deficiencies from conditions such as *septo-optic dysplasia, tumors such as craniopharyngioma, trauma, empty sella syndrome, pituitary dysgenesis, Rathke pouch cysts, or cranial irradiation*

- **Kallmann syndrome, Laurence-Moon- Bardet-Biedl syndrome, and Prader-Willi syndrome**

- Drug abuse, particularly with heroin or methadone,

- Patients with constitutional delay often enter puberty after a short course of sex steroids. If spontaneous puberty does not occur after this treatment or after a second course, the diagnosis of gonadotropin deficiency may be made.
Hypergonadotropic hypogonadism

Elevated gonadotropin levels indicate a failure of the gonads to produce enough sex steroids to suppress the hypothalamic-pituitary axis. These levels are diagnostic for gonadal failure at two periods of time: before 2 to 3 years of age and after the bone age is at or beyond the normal age for puberty to start. If hypergonadotropic hypogonadism is diagnosed, a karyotype should be performed. Potential causes include the following:

- Variants of gonadal dysgenesis: *Turner syndrome, Klinefelter syndrome, Noonan syndrome, pure XX or XY gonadal dysgenesis*
- Gonadal toxins: chemotherapy (particularly alkylating agents), radiation treatment
- Androgen enzymatic defects: 17-alpha-hydroxylase deficiency in the genetic male or female,
- 17-ketosteroid reductase deficiency in the genetic male
- Complete or partial androgen insensitivity syndrome
- *Galactosemia* (in girls only)
- Other miscellaneous disorders: *infections, gonadal autoimmunity, vanishing testes, trauma, surgery, torsion*
Klinefelter syndrome

- the most common cause of testicular failure
- at least one extra X chromosome; the most common karyotype is 47,XXY
- incidence is 1 in 1000 male births

- eunuchoid body proportions are often present from early childhood. Associated features include gynecomastia, tall stature, small testes, low testosterone, and elevated serum gonadotropins. Learning disabilities and behavioral problems may also be present. Many boys with Klinefelter syndrome have spontaneous onset of pubic hair growth, but they fail to progress completely through puberty.

- Testosterone supplementation is indicated in many boys over time, and in some it is required to initiate puberty. Leydig cell function (testosterone production) is variable, but seminiferous tubular function is almost always abnormal. This generally results in infertility, and many of these men are not diagnosed until they are seen in an infertility clinic.
Any consideration of pubertal delay in girls must include the possibility of Turner syndrome. An absent or structurally abnormal second X chromosome characterizes Turner syndrome.

- Incidence: approximately 1 in 2000 live female births. However, the chromosomal abnormality is actually more common than this. Ninety percent or more of conceptuses with Turner syndrome do not survive beyond 28 weeks of gestation, and the 45,XO karyotype occurs in 1 out of 15 miscarriages. In the absence of a second functional X chromosome, oocyte degeneration is accelerated, leaving fibrotic streaks in place of normal ovaries. Because of primary gonadal failure, serum gonadotropin levels rise and are elevated at birth and again at the normal time of puberty.
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Therapy of delayed puberty

- secondary to anorexia, hypothyroidism, illness: treat underlying conditions
- constitutional growth delay: spontaneous puberty
- hypo- or hypergonadotrophic hypogonadism:
  - **boys**: long-term testosterone therapy, watch growth velocity and bone age! depot testosterone esters (enanthate or undecanoate) are used in 25- to 50-mg doses intramuscularly every 3 to 4 weeks for the first 1 to 2 years of therapy. By the second or third year of therapy, the dose is raised to 50 to 100 mg every 3 to 4 weeks. The adult maintenance dose is 200 to 300 mg every 3 to 4 weeks. Alternatively, a transdermic testosterone patch or gel may be used.
  - **girls**: begin with very low-dose unopposed estrogen treatment for 12 to 18 months. Following this period of unopposed estrogen, progesterone is added for 10 to 12 days of each month, and eventually a birth control pill may be prescribed. Progesterone therapy is necessary to counteract the effects of estrogen on the uterus; unopposed estrogen can cause endometrial hyperplasia and carcinoma. Replacement of gonadal steroids in both sexes is also necessary for normal bone mineralization and to prevent osteoporosis and cardiovascular risk.
Management of Turner syndrome

Approximately 10% to 20% of girls with Turner syndrome have some ovarian function at puberty that allows for early breast development. A small percentage of this group will have normal periods, and an even smaller percentage (1% of all girls with Turner syndrome) will actually be fertile.

- Most girls with Turner syndrome require **exogenous gonadal steroid replacement**. Low-dose unopposed estradiol, followed by cycling with estrogen and progestin, allows for development of secondary sexual characteristics. The timing for initiation of estrogen is critical and should be decided by an endocrinologist through discussions with each patient and her family. This decision depends on several factors, including height and psychosocial factors.

- The short stature of girls with Turner syndrome is treated with **GH**. Final adult height in girls with Turner syndrome is related to when GH is initiated, with better outcomes in girls who are started at a younger age. Consequently, early diagnosis of Turner syndrome is essential.

- **Thyroid function** should be checked regularly
Amenorrhea

A girl who has not had menarche by **16 years of age, or within 4 years after the onset of puberty**, is considered to have **primary** amenorrhea.

**Secondary** amenorrhea is diagnosed if **more than 6 months** have elapsed since the last menstrual period, or if more than the length of three previous cycles has elapsed with no menstrual bleeding.

- Progesterone challenge: to assess **oestrogen production**. Girls who are producing estrogen will have withdrawal bleeding after 5 to 10 days of oral progesterone, whereas those who are estrogen-deficient will have very little or no bleeding.

- However, in two situations, girls who have sufficient estrogen will not have withdrawal bleeding: **obstruction or absence of the cervix**. In **Rokitansky syndrome**, maldevelopment of the müllerian structures leads to an absent or hypoplastic uterus or cervix (or both).

- **Complete androgen insensitivity syndrome** (testicular feminization) in a genetic male results in a phenotypic female who has normal breast development because of the aromatization of testosterone to estrogen. The production of antimüllerian hormone in patients with androgen insensitivity syndrome leads to regression of the müllerian structures and thus the absence of a uterus.
Irregular periods

• Amenorrhea in girls who are producing normal or even elevated amounts of estrogen is a manifestation of **anovulatory cycles**.

• Irregular menses may also be a sign of chronic anovulation given that estrogen production, unopposed by progesterone, leads to **endometrial hyperplasia and intermittent shedding**. Because **menarche is normally followed by a period of anovulatory cycles and irregular menses**, many adolescents with a pathologic cause of amenorrhea may be missed.

• It is important to evaluate all girls who do not have regular menses by **3 years after menarche**.

• Chronic anovulation: most common polycystic ovarian syndrome (**PCOS**), a disorder characterized by increased ovarian androgen production. The clinical presentation of PCOS varies and may include amenorrhea, oligomenorrhea, dysfunctional uterine bleeding, hirsutism, acne, or obesity. PCOS is difficult to diagnose in adolescence.
  
  • oligo/anovulation (might be normal in puberty!)
  • biochemical or clinical evidence of hyperandrogenism
  • characteristic US findings
Case 1

A 161/2-year-old girl presented with amenorrhea. She had experienced thelarche and pubarche at 10 years of age, followed by one episode of vaginal bleeding at 12 years old. At that time, she was diagnosed with rhabdomyosarcoma of the right hand. She was prescribed cyclophosphamide, vincristine, and dactinomycin. Three years later, rhabdomyosarcoma appeared in her right breast. Another course of treatment with chemotherapy was administered, which included cyclophosphamide, mesna, and tirapazamine.

She had been in remission from rhabdomyosarcoma for 1 year when she presented with amenorrhea. She had only had one menstrual period.

On physical examination, height was 151.7 cm (3-10 pc), and weight was 53 kg (50th pc). Breasts and pubic hair were in Tanner stage V. Her right breast showed a scar from tumor resection and later breast reconstruction. Her right hand was mildly atrophic and also had a scar from tumor resection. The rest of her physical exam was normal.

What’s the next step in diagnosis?
Serum follicle-stimulating hormone (FSH) measured 66.3 mIU/mL (normal range: 1.5–9); luteinizing hormone (LH) measured 27.4 mIU/mL (normal range: 0.02–12); and estradiol measured 29 pg/mL (normal range for age: 40–410). There were normal circulating levels of thyroid-stimulating hormone (TSH) (0.911 mIU/mL) and prolactin (7.47 ng/mL).

What’s the diagnosis?
How would you treat the condition?
This girl, age 3 years and 7 months, was born full-term. At the age of 9 months she was noted to have a bloody spot in her diaper. This event recurred the following day, and she was taken to see her primary pediatrician. Her pediatrician noted that she had enlarged breasts and a café-au-lait macule on her trunk. Circulating estradiol measured 7.9 ng/dL (normal <1.5), with prepubertal levels of luteinizing hormone (LH) (0.3 mIU/mL) and follicle-stimulating hormone (FSH) (0.03 mIU/mL). She also had a normal prolactin level (10.5 ng/mL). The bone age at chronologic age 9 months was advanced to 2.5 years. By age 2 years and 8 months, she was having vaginal bleeding every 4 to 5 months.

Physical examination at this time revealed the café-au-lait macule and Tanner III breasts and pubic hair. Free thyroxine (FT4) measured 4.2 ng/dL (normal 0.8–2.2) with thyroid-stimulating hormone (TSH) suppressed to less than 0.01 mIU/mL. It was recommended that the patient be treated with the antithyroid medication propylthiouracil and with the aromatase inhibitor testolactone. The family elected not to proceed with these treatments.

She presented to our clinic at the age of 3 years and 7 months. At this time, she had progressive breast development and was still having vaginal bleeding every 5 months. She did not have hirsutism, adult body odor, acne, or male-pattern baldness. She had dry hair and skin, but no temperature intolerance, constipation, or sleep disturbance. She had always been tall for her age. She had no breast discharge, headaches, vision disturbances, or symptoms of hypoglycemia.
On physical examination, height was **111.7 cm (+3.5 SD)**, and weight was 18.8 kg (between the 90th and 95th percentiles). **Pulse was 150** and blood pressure was 134/61. A large café-au-lait macule extended over the right side of the trunk to the midline of the abdomen and to the midline of the back. It had irregular borders (“coast of Maine”). The thyroid gland was enlarged to twice normal size and was firm without nodules. Breasts were in late Tanner stage III, and pubic hair was in early Tanner stage II.

Sodium was 136 mEq/L, potassium was 4.2 mEq/L, chloride 110 mEq/L, and bicarbonate 21.7 mEq/L. Glucose was 5.1 mmol/L. BUN was 7 mg/dL, and creatinine was 26.5 umol/L. Calcium was 2.37 mmol/L. Phosphorus was slightly low at 1.1 mmol/L. Liver function tests were normal except for total **bilirubin** mildly increased at 1.1 mg/dL, with a normal direct fraction of less than 0.1 mg/dL. Alkaline phos- phatase was elevated at 594 IU/L.

The patient’s **gonadotropins were suppressed** to less than 0.05 IU/L. **Estradiol** was elevated at **26 ng/dL** (normal range for age: <1.5; normal range for Tanner stage III: 10–14.4). Total **thyroxine** was elevated at **14.1 g/dL**, and triiodothyronine measured 380.8 ng/dL (normal 119–218). The **TSH** was suppressed to less than 0.01 IU/mL. **Bone age was 10 years and 6 months** at the chronologic age of 3 years and 7 months.

Bone survey revealed a **ground-glass appearance in the right side of the mandible**, some **sclerotic changes in the base of the skull** in the region of the maxilla, and lucent and sclerotic areas in both **femoral necks**, particularly on the right side. There was also a small lesion in the right mid-humerus, consistent with polyostotic fibrous dysplasia.

**What’s the diagnosis?**

**What additional diagnostic tests are required?**

**What’s the appropriate therapy?**
Case 3

This boy, age 4 years and 4 months, presented with precocious pubertal development. He had a significant increase in his growth velocity over the past 2 years. As an infant, he had been in the 50th percentile for length. From the age of 18 months, his length percentile steadily increased. At age 4 years and 4 months, he was wearing clothes appropriate in size for a 7-year-old boy. At age 3 years and 8 months, the patient developed pubic hair, increased oiliness of skin and hair, and aggressive behavior. At 4 years of age he developed acne over his nose and upper back and adult body odor.

He has not had headaches, seizures, or vision disturbance. There is no family history of early puberty, pituitary, or thyroid disease.

On examination, height was 126.4 cm (+5 SD above the mean, 50th percentile for a boy of 7 years and 9 months). Weight 31.5 kg (3.8 standard deviations above the mean, 50th percentile for a 9-year-old boy). Acne was present over the bridge of the nose, forehead, and on the upper back. Hair was oily. The eyes were normal, as was the thyroid. The neurologic examination was normal. The penis was enlarged to 11.0 cm in length. The testes measured 4.5 cm in length (25 mL) bilaterally. Pubic hair was in Tanner stage III.

What’s the most likely diagnosis?
What’s the next step in diagnosis?
Bone age: chronologic age is 4 years and 4 months. The bone age (Greulich and Pyle) is estimated to be 9 years. One standard deviation for a male this age is 7.8 months.

Insulin-like growth factor I (IGF-I): 333.7 ng/mL (normal 58–209)
Insulin-like growth factor binding protein 3 (IGF-BP3): 2.7 mg/L (normal 0.8–3.0)
Human chorionic gonadotropin (HCG) quantitative: < 2 mIU/mL
Testosterone: 280 ng/dL (within range for Tanner stage III–IV male; prepubertal range 3–10)
Thyroid-stimulating hormone (TSH): 1.91 IU/mL (normal 0.5–5.0)
Free thyroxine (FT4): 1.53 ng/dL (normal 0.8–2.2)
Triiodothyronine: 177 ng/dL (normal 105–269)
Follicle-stimulating hormone (FSH): 1.6 mIU/L (normal 1–3.2)
Luteinizing hormone (LH): 1.56 mIU/mL (normal 0.07–0.3)
Prolactin: 39.6 ng/mL (normal 2–13)
Growth hormone: 0.71 ng/mL (normal 0.1–6)
Serum sodium: 139 mEq/L (normal 134–146)
Cortisol (in a.m.): 9.5 g/dL (normal 3–21)

What’s the diagnosis?
How is it treated?
Case 4

This boy, age **3 years and 9 months**, was referred for precocious puberty. He had pubarche 6 months prior to presentation. His **genitalia** had always seemed to be larger than his older brother’s genitalia; they had increased in size over the 4 to 6 months prior to presentation. He also had recent **acceleration of growth** in height. He did not have acne, adult body odor, breast enlargement, skin lesions or pigment abnormalities, headache, breast discharge, polyuria, or polydipsia. His energy had been normal. He had no prostration with intercurrent illness, orthostasis, salt craving, or symptoms of hypoglycemia.

The patient was born of an uncomplicated, full-term gestation. One year prior to presenting with early puberty, he sustained a **concussion after jumping out of his sister’s crib**; computed tomography of the head was **negative**.

The family history showed that the mother had menarche at 12 years of age, and the father’s age at puberty was 13 years. The maternal grandmother had thyroid disease. There was no history of precocious puberty in the family.

On examination, height was **107.4 cm (95th pc)**, and weight was **17.9 kg (75th to 90th percentile)**. The skin had no café-au-lait spots or other pigmentary abnormalities. The eye examination was normal. The thyroid was normal. **Pubic hair was in Tanner stage II**. The penis measured **9 cm in stretched length** and **2.5 cm in diameter**. The **left testis** had a volume of **2 to 3 mL** and the **right** had a volume of **4 to 5 mL**.

What’s the most likely diagnosis?

What’s the next step in evaluation?
Bone Age: chronologic age is 3 years and 9 months. According to standards of Greulich and Pyle, the bone age is 6 years. One standard deviation for a male this age is 6 months.

**Testosterone:** 179.7 ng/dL (normal < 10 ng/dL)
Follicle-stimulating hormone (**FSH**): 0.5 mIU/mL (normal 1–3.2)
Luteinizing hormone (**LH**): < 0.10 mIU/mL (normal 0.7–3)
Human chorionic gonadotropin (**HCG**): < 2 mIU/mL (normal < 2)
Fetoprotein (**AFP**): 4.9 ng/mL (normal 0–8.9)

**Androstenedione:** 28 ng/dL (normal 5–115)
Dehydroepiandrosterone sulfate (**DHEAS**): < 15 ng/dL (normal < 25)
**17-hydroxyprogesterone:** 26 ng/dL (normal 4–115)
Free thyroxine (**FT4**): 1.53 (normal 0.8–2.2)
Thyroid-stimulating hormone (**TSH**): 3.69 (normal 0.5–5)

What’s the diagnosis?
How is it treated?
Case 5

This girl, age **17 years and 3 months**, presented for evaluation of primary amenorrhea. She had thelarche at **9 to 10 years of age and pubarche**, and appearance of acne, adult body odor, and axillary hair at 12 years of age. She had **not had menarche**. She had a long history of **obesity**, with weight greater than the 97th percentile since the age of 3 years, height at the 50th to 90th percentiles, and weight for height greater than the 95th percentile. She did not have galactorrhea, hirsutism, male pattern hair loss, or lowering of the pitch of her voice.

She had normal temperature tolerance and energy. There had been no easy bruising, striae, or muscle weakness.

Her mother’s age at menarche was 11 years old. A paternal aunt had menarche at 16 years of age. There was no family history of menstrual irregularity, infertility, hirsutism, pituitary tumors, kidney stones, hypercalcemia, or severe peptic ulcer disease.

On examination, height was 166.2 cm (50th to 75th percentile), and weight was 81 kg (90th to 95th percentile). Body mass index (BMI) was 29.3 kg/m$^2$. The skin had nonviolaceous striae over the abdomen and acanthosis nigricans of the neck and axillae. There was no hirsutism. The eye examination was normal, including visual fields by confrontation, extraocular movements, and ocular fundi. The thyroid gland was normal. Breasts were in Tanner stage V with no discharge. Pubic hair was in Tanner stage III. The clitoris and vagina were normal.

What’s the next step in evaluation?
Follicle-stimulating hormone (FSH): **0.9** mIU/mL (normally menstruating females 1.5–33.4)
Luteinizing hormone (LH): **0.1** mIU/mL (normally menstruating females 0.5–76.3)
Thyroid-stimulating hormone (TSH): **1.339** IU/mL (normal 0.7–5.7)
Free thyroxine (FT4): **0.8** ng/dL (normal 0.6–2)
**Prolactin:** **164.9** ng/mL
**Hemoglobin A1c:** **5.5%**
**Chromosomes 46, XX**
**17-OH progesterone:** **12** ng/dL
**Testosterone, total:** **33** ng/dL (normal 5–40)
**Testosterone, free:** **3.07%** (normal for adult female 0.8–1.4%)
**Testosterone, free dialysis:** **10.1** pg/mL (normal 0.2–3.2)

What’s the diagnosis?
How is it treated?
Case 6

The patient was born of a full-term gestation and normal vaginal delivery. Her birth weight was 3100 g. At age 2 years and 9 months, height was in the 25th percentile and weight was in the 10th percentile. By age 4 years and 8 months, height was in the 10th percentile and weight was between the 10th and 25th percentiles. **Height** standard deviation score fell to **2.7 SD** below the mean by the time of her presentation to a pediatric endocrinologist at age **9 years and 10 months**. She had normal results of studies of urinalysis, complete blood count, erythrocyte sedimentation rate, blood chemistries, insulin-like growth factor I (IGF-I), IGF-BP3, thyroxine (T4), and thyroid-stimulating hormone (TSH). **Karyotype was 46X,i(X)(910).** The follicle-stimulating hormone (**FSH**) measured **6.5 mIU/mL**, (normal: 1–6) and luteinizing hormone (**LH**) measured **0.18 mIU/ml** (normal: 0.02–0.3). Echocardiogram and ultrasound of the kidneys were normal. The patient presented to our clinic at age **10 years and 1 month** for the assessment of her appropriateness of **growth hormone treatment**.

She had not had symptoms of dysfunction in the thyroid-stimulating hormone (TSH), antidiuretic hormone (ADH), adrenocorticotropic (ACTH), prolactin, or gonadotropin axes. She had not had gastrointestinal symptoms or headache or vision problems.
Her father’s height was 190 cm; mother’s height was 168 cm. Her mother had menarche at 12 years of age and had hypothyroidism. **Hypothyroidism** had been present in the maternal grandmother and maternal-maternal great grandmother.

On examination, height was **120.8 cm (-2.8 SD)**. Weight was 21.8 kg (-2.6 SD). Blood pressure was 97/66; pulse was 98. The skin, eyes, ears, palatal arch, thyroid gland, neck, and abdomen were normal. The chest was clear. The heart had a 2/6 systolic ejection murmur at the left lower sternal border. There was cubitus valgum on the left and incomplete elbow extension on the right. The **4th and 5th metacarpals were short** bilaterally. Deep tendon reflexes were normal. The spine was normal. Breasts and pubic hair were in **Tanner stage 1**.

Growth hormone treatment was started at age 10 years and 1 month. At the time of her most recent follow-up at age **13 years and 11 months**, the patient’s **height was -2.7 SD**. Breasts were in **Tanner stage 1, while pubic hair was in Tanner stage III**. She had not had menarche.

What’s the diagnosis?

What are the main points of the endocrine care?