

# *Different From My Friends*

## Facilitator's Guide

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**Topic:** Turner's Syndrome and Delayed Puberty

**Abstract:**

Questions about the timing and sequence of pubertal development are common in primary care practice. Health care providers need to know the normal stages of pubertal development and when puberty is considered delayed. Clinicians need to be able to initiate the evaluation of an adolescent with pubertal delay. This case presents the story of Beth, a nearly 13 year-old-girl with no signs of pubertal development accompanied by short stature. This constellation should prompt a consideration of the differential diagnosis and will point in the direction of Turner's Syndrome.

**Goal:**

To provide learners with a basic understanding of the normal pubertal sequence and causes of delayed puberty.

**Objectives:**

By the end of the session, learners will be able to:

1. List the stages of normal pubertal development and the age of initiation of puberty.
2. List the differential diagnosis for pubertal delay.
3. Initiate the evaluation of an adolescent with short stature and pubertal delay.

**Prerequisite Cases:** N/A

**Related Cases:**

"The Shortest in the Class" (Turner's Syndrome and Short Stature)\*\*

"Will I Ever Get My Period" (Growth and Chronic Disease)

"Timmy and the 'Big Kids'" (Constitutional Short Stature)

"Normal vs. Abnormal Patterns" (Understanding Growth)

**Themes:**

Adolescent Health, Growth in Children and Adolescents

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\*\*Editor's note: The case narratives of the two Turner's syndrome cases are similar, but "Different From My Friends" focuses on the evaluation of delayed puberty while "The Shortest in the Class" focuses on the assessment of short stature. Facilitators should choose the case most appropriate for their group of learners.



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**Key Words:**

Puberty, delayed puberty, Turner's Syndrome, growth disorders, normal pubertal development

**Bright Futures Core Concepts:**

While all of the Core Concepts are included in each case, this particular case can be used to highlight communication, partnership, and prevention/health promotion.

**Materials Provided:**

- Facilitator's Guide
- 3-part Case Narrative: Part I, Part II, Epilogue
- Handout #1: Female Pubic Hair Development
- Handout #2: Female Breast Development
- Handout #3: Beth's Growth Chart
- Handout #4: Beth's Baseline Test Results
- Bibliography

**Facilitator Preparation:**

Facilitators should thoroughly review this guide and the other materials provided. Because this case is virtually the same as "The Shortest in the Class," Turner's Syndrome and Short Stature, facilitators should review both cases and decide which case would be most useful/appropriate for their learners.

At the end of the guide we have included a section entitled, "**Independent Learning/Prevention Exercises**," that will further stimulate group and individual education on this topic.

**Suggested Format for a One Hour Session:**

**We anticipate that case facilitators will modify implementation of the case session to best fit their educational setting and learners. For detailed recommendations on case facilitation, please see the previous chapter entitled, "A Brief Guide to Facilitating Case Discussion."**

**Introduction:** Beth is a 12 11/12 year-old patient with no signs of pubertal development and short stature. A challenge is that there is little documentation of her past growth velocity or previous medical care as she has not seen a pediatrician in several years. The learner is forced to rely on information from the parents and current clues from today's history and physical examination.

The lack of pubertal development, short stature, and normal appetite and weight should prompt consideration of Turner's Syndrome. The clinician will need to obtain the pertinent history, perform a physical examination, and obtain laboratory testing. The patient will need growth hormone and sex steroid replacement to complete optimal growth and pubertal development.

**Open the Discussion: Introduce the case title and the session goal. Explain that this will be an interactive case discussion and not a lecture. Distribute Part I of the case and ask one or more of the participants to read it aloud.**

### **Part I**

Beth is a 12 11/12 year old girl whose parents are concerned about Beth's short stature and lack of development. They claim that she has always been "*the shortest in the class*" but "*eats good*" and is not underweight for her height. She has a good energy level and appetite. She is a B+ student and active in sports. She has not seen a physician in 4 years because her family has no health insurance.

Beth looks like a healthy young adolescent. She would like to be a "*little taller,*" but she is very worried about why she has not had any breast development. "*All my friends are developed, and I get teased in gym class when I undress. My mom said she got her period when she was 12.*"

**Following this reading, ask all participants "*So what do you think about this case? What would you like to focus on during our discussion today?*" List agenda items on a blackboard or flipchart. Then use the questions below to guide the discussion. Remember that the key to successfully leading a small group is facilitation of the discussion rather than lecture. Draw as many participants as possible into the discussion. Allow silences while group members think about questions. Present material from the discussion guide only when needed to complement or redirect the group discussion.**

### **Guiding Questions for Discussion:**

**What additional information would you like to know about Beth?** To assess whether the parents' concerns regarding the short stature are accurate and legitimate, one would need to find out more information about the patient's *past medical history*. Has the patient had stigmata of a chronic illness that might be affecting her growth? A *growth chart* needs to be constructed with as many data points as are available (to determine if growth ceased at a specific point or if she has remained consistently on a single, delayed curve). Is she on any medications that might affect her metabolism and her growth? Is there a history of head trauma or a surgery that might have affected the hypothalamic-pituitary area, and growth hormone (GH)-secreting neurons? Is she having headaches, visual changes, vomiting, or other signs of a central process? *Family history* would also be important (*e.g.* history of short stature, history of miscarriages, age of pubertal onset in each parent, pubertal delay in other family members, etc), including the heights of both parents to determine a *mid-parental height (MPH)* (father's height - 5 inches, averaged with mother's height for a girl). The MPH will enable one to see how close she is following her genetic potential. Lastly, she needs a thorough *physical examination* to assess for stigmata of a chronic disease, of a known syndrome (*e.g.* chondrodysplasia or Turner's syndrome) or signs of a central process (*e.g.* papilledema, etc.)

The assessment should also include questions about other stressors, family constellation, intensity of sports participation, concerns about weight and nutritional intake, and how much discussion she has had at home about her pubertal development.

*Bright Futures Guidelines for Health Supervision* list screening questions that clinicians may find useful:

- Who do you live with?
- How do you get along with family members?
- How often do you miss school?
- What activities and sports are you involved in?
- How do you feel about your weight? Are you trying to change your weight? How?
- What do you usually eat in the morning? At noon? In the afternoon? In the evening?
- Has anyone talked with you about what to expect as your body develops? Have you read about it?
- Have you started your period yet?

**What is the normal sequence of puberty (for breast development, pubic hair and growth in a female patient)?** The age at which puberty begins in a normal girl can vary widely. Breast development usually begins before pubic hair development. Pubic hair is the first sign of pubertal development in 15-30% of girls; pubic hair development precedes breast development more commonly in African-American girls than white girls. The breast and pubic hair maturation should be staged separately to allow for recognition of discrepancies of development. The average age with standard deviation (SD) for attainment of pubertal milestones in North American girls is age  $10.9 \pm 1.0$  years for breast budding (Tanner II; also termed Sexual Maturity Rating 2) and  $11.2 \pm 1.1$  years for pubic hair development (Tanner II). However, a recent study of 17,000 girls seen in pediatric practices suggested an earlier age of onset. Herman-Giddens and colleagues<sup>3</sup> noted that among 8-9 year olds 7.7% of white girls and 34.3% of African-American girls had Tanner stage 2 or greater pubic hair and 5% of white girls and 15.4% of African-American girls Tanner 2 or greater breast development. Remind learners that breast development is controlled predominantly by ovarian estrogen secretion while pubic hair development is stimulated by secretion of adrenal androgens. The growth spurt occurs during early adolescence in a girl, typically occurring between Tanner breast stage II and III with peak height velocity at an average age of 11.5 years. Menarche occurs at a mean age of  $12.7 \pm 1.0$  years, about 2 to 2 1/2 years after the onset of breast development and on the downslope of the height velocity curve.

**Is Beth's puberty delayed?** As noted above, breast development is typically the first sign of puberty in a female. A girl who has experienced no breast development or other signs of puberty by age 13 years is 2 standard deviations from the normal age and has delayed development. Among girls 12-13 years old, 96% of white girls and 99% of African-American girls had breast development, and 92% of white girls and 99% of African American girls had pubic hair development.<sup>3</sup> While our patient is beyond the average age of pubertal onset, she has not yet reached the age of 13 years, 2 SD beyond the normal threshold age. *However*, as she is *close* to that age and has no pubertal development in the setting of short stature, one's concern should be raised. The onset of puberty is more closely related to an individual's bone age than chronologic age.

Therefore, a bone age assessment can be helpful in determining the cause of delayed puberty and growth deficiency.

**Distribute Handout #1: Female Pubic Hair Development and Handout #2: Female Breast Development which outline normal female pubertal development as you distribute Part II of the case. This will remind the facilitator to review Tanner staging of pubertal development.**

**Distribute Part II of the case and have participant(s) read it aloud. Distribute Handout #3: Beth's Growth Chart.**

## Part II

Beth's past medical history is remarkable for recurrent otitis media as a child. She was the product of a full-term gestation after an uncomplicated pregnancy; her birthweight was over 7 pounds and her length was 21 inches. She met normal developmental milestones, and her only surgery was placement of tympanostomy tubes at age 2 years for the recurrent otitis media. She was admitted only once at age 1 year for observation after a febrile seizure. She is taking no medications or vitamins.

On a growth chart, she is in the 5-10 percentile for weight and below the 5 percentile for height. Her mother's height is 62" and the father's height 69"; therefore, the patient's mid-parental height is 63".

On physical exam, she is young-appearing and healthy.

VS: BP 100/64, Pulse 76.  
Weight is 35 kg (77 pounds).  
Height 132.4 cm (52 inches)

Skin: pigmented nevi on back, anterior neck, and right axilla.

HEENT: benign

Neck: no goiter or lymphadenopathy

Breast: Tanner I

Lungs: clear

Heart: normal sinus rhythm, I/VI systolic ejection murmur along left sternal border. No gallop or rub.

Abdominal: soft, no hepatosplenomegaly

Genitourinary: Tanner I pubic hair. Normal external genitalia. Rectoabdominal exam revealed a small cervix and no adnexal masses. Stool negative for occult blood.

Neurologic: nonfocal, normal reflexes, without delayed relaxation.

### **What parts of the physical examination/health assessment are particularly important for this evaluation? Should you perform a pelvic examination?**

The important elements are measurements of height, weight, Body Mass Index (BMI), blood pressure, notation of acne/dermatoses, palpation of the thyroid, and Tanner staging/sexual maturity rating.

An external genital examination is important to assure a normal clitoris, labia, hymen and presence or absence of estrogen effect on the vaginal mucosa. A recto-abdominal examination may be helpful to confirm normal internal anatomy and particularly to check stool for occult blood but it is optional. However, an internal examination is not needed because vaginal and uterine anomalies cause amenorrhea or pain, not lack of pubertal

development. Thus the clinician should concentrate on signs of central nervous system (CNS) problems and ovarian causes of the pubertal delay. In contrast, the patient with full pubertal development and no menses needs an internal examination to exclude a genital anomaly (mullerian anomaly or androgen insensitivity syndrome) or obstruction (imperforate hymen, transverse vaginal septum).

**What is the differential diagnosis? (Then, can you narrow down the differential based on the information you have obtained?) It is often helpful to put a stick figure on the blackboard (see next page) to help learners organize their differential diagnosis of *delayed puberty* (with no signs of virilization or androgen excess).**

**Differential Diagnosis:**

CNS causes:

- Hypogonadotropic hypogonadism (low to normal FSH, LH levels)
  - Chronic disease, especially those associated with malnutrition (cystic fibrosis, Crohn's, celiac disease)
  - Kallmann's syndrome
  - CNS tumors
  - Lawrence-Moon-Biedl, Prader-Willi syndromes
  - Pituitary causes - tumor (e.g., prolactinoma, germinoma, etc.)
    - infiltrative disease (sarcoid, tuberculosis, Histiocytosis X, CNS leukemia), hemochromatosis, head trauma, postpartum necrosis, "empty sella"
  - Endocrinopathies, including hypothyroidism, diabetes mellitus, Cushing's syndrome (including iatrogenic from steroid therapy)
  - Depression
  - Physiologic delay
  - Eating disorders, athletic competition (may be overlap between these two entities)

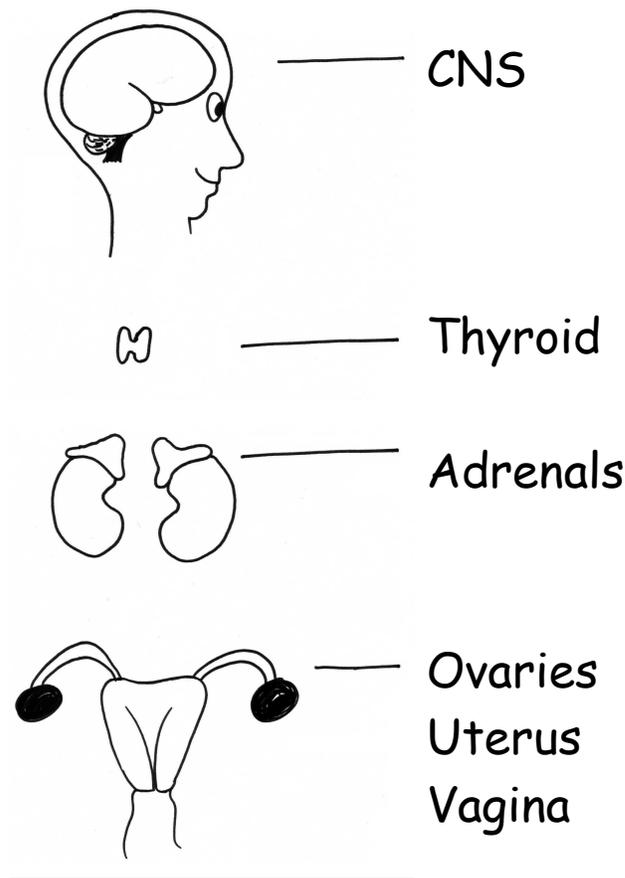
Thyroid: hypothyroidism, hyperthyroidism

Adrenal: Cushing's syndrome, Addison's disease

Ovaries:

- Hypergonadotropic hypogonadism (high FSH and LH levels)
  - Gonadal dysgenesis
  - Ovarian failure from radiation or chemotherapy
  - Autoimmune oophoritis
  - Other -galactosemia, myotonia dystrophica, Trisomy 21, sarcoidosis, ataxia telangiectasia; ovarian hemorrhage, torsion, removal or destruction; oophoritis; 17-hydroxylase deficiency

Example Blackboard Drawing:



Beth has short stature and delayed puberty, leading the learner to consider gonadal dysgenesis (Turner's Syndrome). She also has multiple nevi and a history of otitis media. In Lippe's series of girls with Turner's Syndrome,<sup>4,5</sup> the incidence of gonadal failure was 96% and short stature 100%.

**What baseline tests would you want to order (if any)?**

The learners should generate a list of tests they would order using the differential diagnosis generated. It is helpful to list all of the possible tests and ask participants to vote on the top four tests they would obtain first. Then reveal the lab results for those tests one at a time in the order listed below, and decide what second and third steps are.

Besides screening CBC and chemistries to exclude an unsuspected chronic illness, the most important endocrine tests are a TSH level (to exclude hypothyroidism) and a FSH level to determine if the etiology is hypothalamic-pituitary (low or normal FSH) or secondary to ovarian failure (high FSH). If hypothyroidism could occur because of a CNS process, then other thyroid functions tests (T4) should be obtained. Prolactin level is drawn if FSH is low. If FSH is high, a karyotype and other studies to determine the etiology of ovarian failure should be ordered. Hand and wrist radiograph for bone age

helps to estimate final height and to ascertain if bone age is delayed more than height age (common with hypothyroidism). Give out the diagnostic karyotype data *last*.

**CBC, Sedimentation rate (ESR) Liver function tests, electrolytes, BUN, creatinine, glucose, albumin, total protein, Ca, phosphorus - NORMAL**

**Thyroid function tests:** T4 8.8 µg/dl, TSH 2.6 µU/ml, TBGI 0.93  
NORMAL

**FSH** 167.3 IU/L - MARKEDLY elevated

**Bone age** 10 years (one standard deviation is 10 months) - DELAYED

**Chromosomes (karyotype):** 45,X/46,XX. Mosaic karyotype with two cell lines, consistent with diagnosis of Turner's variant or mosaic.

The elevated FSH level is consistent with gonadal failure. Turner's syndrome or variant are highest on differential list and the karyotype has yielded the critical information.

**Distribute Handout #4: Beth's Baseline Test Results, after the group has reviewed the tests results individually. Distribute the Bibliography page and Epilogue. Ask someone to read the Epilogue aloud.**

#### **Epilogue**

This patient is currently age 14 years, 6 months. She was begun on growth hormone therapy immediately after the diagnosis of Turner's mosaic was made. She has shown a good response to therapy with a marked acceleration of her growth velocity. The patient has been quite self-conscious over the past 6 months as her "*body is different from all of my classmates.*" Because of her age and concern about lack of pubertal development, low-dose estrogen therapy was recently initiated. She is pleased with the breast development she is experiencing and is more self-confident. Her parents have joined the Turner's Syndrome Society.

#### **Discuss the management plan for this patient.**

*Growth:* The timely management of growth failure will affect many aspects of Turner's syndrome, including the age at which estrogen replacement is begun, socialization and academic achievement. Height should be plotted on growth curves specific for Turner's syndrome patients. Although these patients are not GH-deficient, they respond well to exogenous GH (recombinant human GH). GH therapy should be initiated by a pediatric endocrinologist as soon as the patient falls beneath the 5 percentile. Studies have documented short-term growth acceleration following treatment with GH, either alone or in combination with low doses of oxandrolone (an oral anabolic steroid). Rosenfield *et al.*<sup>9</sup> followed 62 American girls with Turner's syndrome over a 6-year period. Of the 17 recipients of GH alone, 14 (82%) exceeded their original projected adult height. Of the 45 recipients of combination GH plus oxandrolone, 41 (92%) exceeded their projected adult height. The mean height of the patients at the study's conclusion was 151.7 cm or 5 feet. Based on this data, combined with equally impressive outcomes from other studies, GH therapy has become the standard of care for these patients in this and many other countries. An adult height of > 150 cm, the lower limit of normal for American women, is now an attainable goal for most girls with Turner's syndrome who are treated with GH therapy during childhood for a minimum of 6 years.

*Sex hormone replacement:* Sex steroid replacement (estrogen) is typically begun at the age of 14-15 years to promote secondary sex characteristic development. One must initiate this therapy cautiously as estrogen will accelerate maturation of the epiphyses and, if begun prematurely, can decrease a patient's final height. A physician should discuss the issue of estrogen replacement with each patient and her family as psychological issues around puberty also contribute to the decision of when estrogen is initiated. Sex steroid replacement, such as conjugated estrogens (Premarin 0.3 mg daily or every other day), or other low dose oral, percutaneous or injectable estrogen, is prescribed for 6 to 12 months. The dose of conjugated estrogen is increased to 0.625 mg daily with the progestin medroxyprogesterone added in cyclic doses. Maintenance programs include conjugated estrogen and progestin (e.g., PremPhase), estradiol patches and progestin, or low dose oral contraceptives.

**Refer back to group's learning agenda and summarize the key teaching points that were made. This will give the group a sense of accomplishment, and emphasize the important messages. Suggest further sources of reading or other information if there are agenda items that were not covered in the discussion.**

**Independent Learning/Prevention Exercises:** Facilitators may wish to assign "Independent Learning/Prevention Exercises" to the group, particularly if time constraints hinder the completion of the case. The following list includes suggestions to explore the available community resources that focus on Turner's Syndrome, as well as other areas of pertinent interest that can be integrated during or after the session. If the exercise is done in the absence of the facilitator, learners should take notes on their experience, then discuss with a faculty member for feedback.

1. Find out about the Turner's Society and explore their web site, newsletter, and consumer guides.
2. Invite the parents and/or patient (older adolescent or adult) with Turner's Syndrome to speak to the group.

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**Part I**

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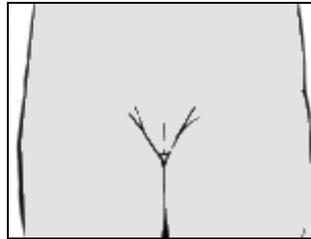
Neurologic: nonfocal, normal reflexes, without delayed relaxation

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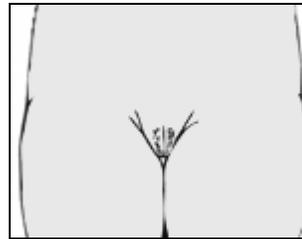
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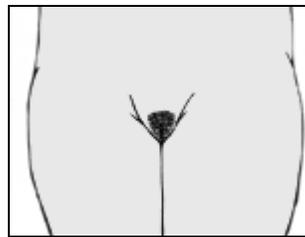
***Different From My Friends***  
**Handout #1: Female Pubic Hair Development**



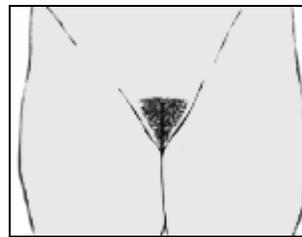
**Stage 1**



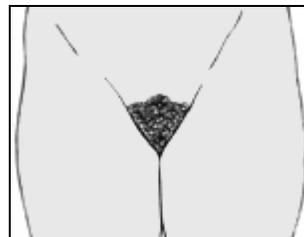
**Stage 2**



**Stage 3**



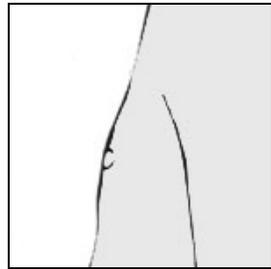
**Stage 4**



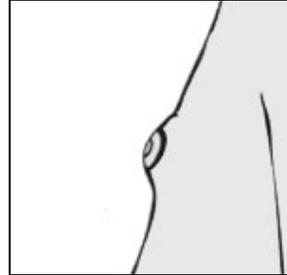
**Stage 5**

Female pubic hair development. *Tanner stage 1:* Prepubertal, with no pubic hair. *Tanner stage 2:* Straight hair is extending along the labia, and between rating 2 and 3, begins on the pubis. *Tanner stage 3:* Pubic hair has increased in quantity, is darker, and is present in the typical female triangle, but in smaller quantity. *Tanner stage 4:* Pubic hair is more dense, curled, and adult in distribution, but is less abundant. *Tanner stage 5:* Abundant, adult-type pattern; hair may extend on to the medial aspect of the thighs.

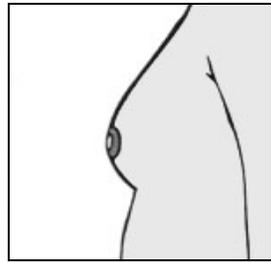
***Different From My Friends***  
**Handout #2: Female Breast Development**



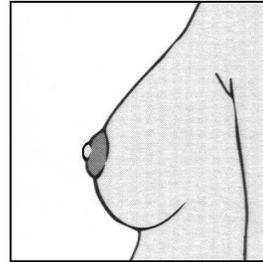
Stage 1



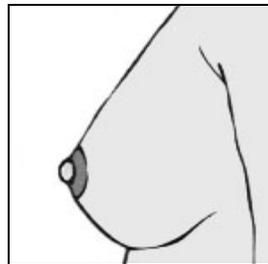
Stage 2



Stage 3



Stage 4



Stage 5

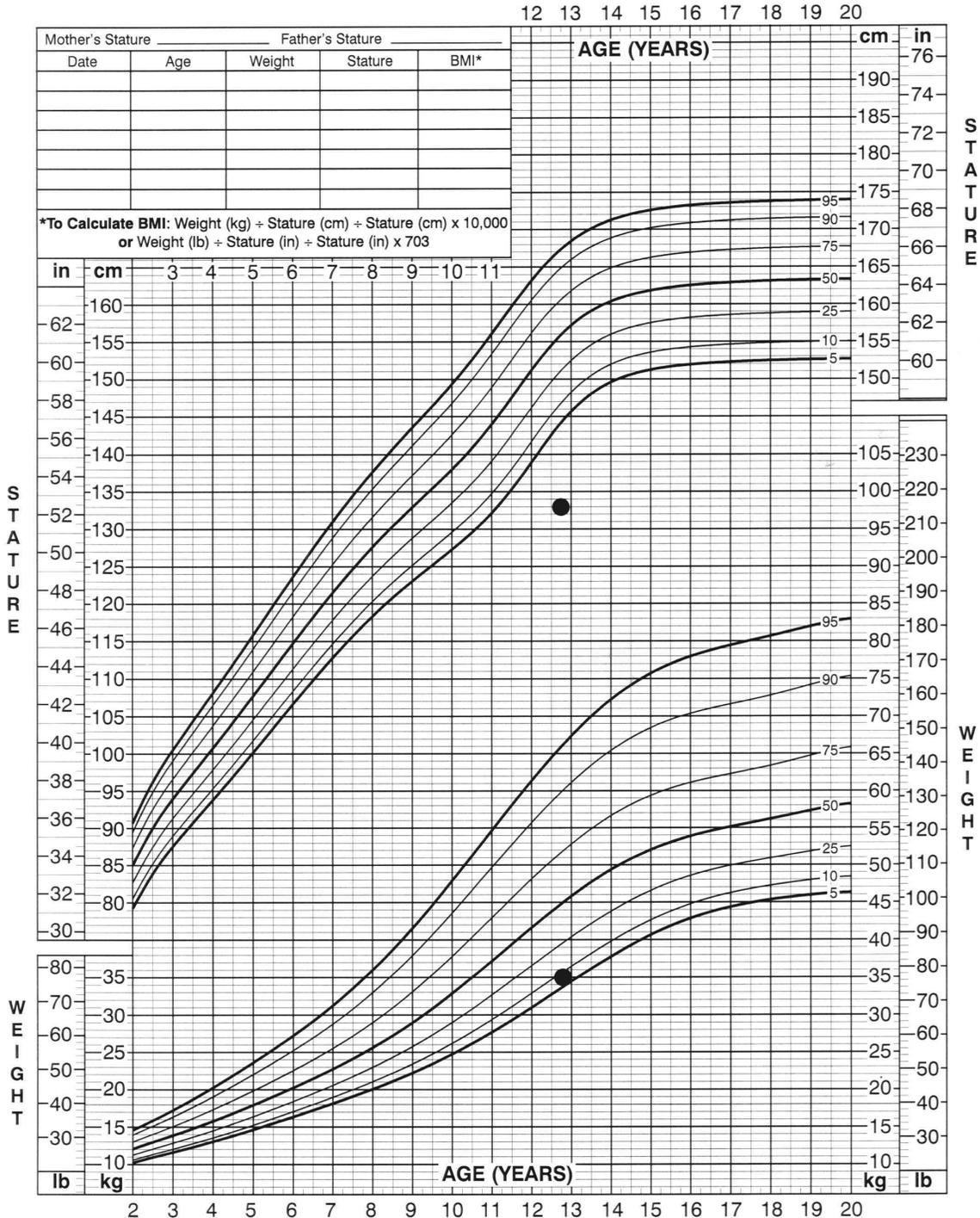
Female breast development. *Tanner stage 1:* Prepubertal, with elevation of papilla only. *Tanner stage 2:* Breast buds appear. Areola is slightly widened and projects as a small mound. *Tanner stage 3:* Enlargement of the entire breast with no protrusion of the papilla or of secondary mound. *Tanner stage 4:* Enlargement of the areola and papilla as a secondary mound. *Tanner stage 5:* Adult configuration of the breast with protrusion of the nipple. Areola no longer projects separately from remainder of breast.

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## Handout #3: Beth's Growth Chart

2 to 20 years: Girls  
 Stature-for-age and Weight-for-age percentiles

NAME Beth  
 RECORD # \_\_\_\_\_



Revised and corrected November 28, 2000.  
 SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>



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**Handout #4: Beth's Baseline Test Results**

- **CBC, Sedimentation rate (ESR) Liver function tests, electrolytes, BUN, creatinine, glucose, albumin, total protein, Ca, phosphorus - NORMAL**
- **Thyroid function tests:** T4 8.8 µg/dl, TSH 2.6 µIU/ml, TBGI 0.93 - NORMAL
- **FSH 167.3 IU/L - MARKEDLY elevated**
- **Bone age** (chronologic age 12 11/12 years): 10 years (one standard deviation is 10 months) - DELAYED
- **Chromosomes (karyotype):**  
45,X/46,XX. Mosaic karyotype with two cell lines, consistent with diagnosis of Turner's variant or mosaic.

The elevated FSH level is consistent with gonadal failure. Turner's syndrome or variant are highest on differential list and the karyotype has yielded the critical information.

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### **Bibliography:**

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11. Tanner JW, Davies PWS. Clinical longitudinal standards for height and height velocity for North American children. *Journal of Pediatrics* 1985;107:317-29.

### **Selected Readings (Annotated):**

**Saenger P. Turner's Syndrome. *New England Journal of Medicine* 1996;335:1749-54.**

An overview of clinical presentation and associated problems of Turner's Syndrome.

**Emans SJ, Laufer MR, Goldstein DP. *Pediatric and Adolescent Gynecology*, fourth edition. Philadelphia: Lippincott, Williams and Wilkins; 1998.**

Chapter 4 covers pubertal development in girls and Chapter 6 provides a simplified approach to the diagnosis and management of delayed development.

**American Academy of Pediatrics. Committee on Genetics. Health supervision for children with Turner's Syndrome. *Pediatrics* 1995;96:1166-73.**

These are guidelines for general health supervision of children and adolescents with Turner's Syndrome. The type of imaging recommended and the periodicity of cardiac screening is likely to be changed.

### **Educational Resources on the World Wide Web**

*Turner's Society of the United States*, 14450 T. C. Jester, Suite 260, Houston, TX 77014 (Telephone 832-249-9988, 800-365-9944; Fax 832-249-9987). A resource for families and patients. Patients can order the guide for families (reference #6), subscribe to the newsletter, and join local and national groups.

<http://www.Turner-syndrome-us.org>

*Center for Young Women's Health Resource Center*, Children's Hospital, Boston

This site provides valuable patient information written for teens on adolescent health topics.

<http://www.youngwomenshealth.org>