Will I Ever Get My Period?
Facilitator's Guide

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Topic: Growth and Chronic Disease

Abstract:
Sarah is a 13 6/12 year-old patient with an arrest of pubertal development, weight loss and decelerated growth velocity. Differentiating between patients who are underweight for height and overweight for height is an important first step in a cost effective evaluation. The evaluation of a girl who is underweight for height or has lost weight should prompt an evaluation for a systemic disease associated with undernutrition such as inflammatory bowel disease, anorexia nervosa, malabsorption (e.g. celiac disease) or other chronic disease.

Goals:
To provide learners with a basic understanding of the normal pubertal sequence and causes of delayed puberty, and a systematic approach to the patient with delayed pubertal development.

Objectives:
By the end of the session, learners will be able to:
1. Describe the stages of normal pubertal development and the age of initiation of puberty in girls.
2. Describe the differential diagnosis for pubertal delay in girls.
3. Initiate the evaluation of an adolescent with arrest in pubertal development.

Prerequisite Cases: N/A

Related Cases:
"Normal vs. Abnormal Patterns" (Understanding Growth)
"The Shortest in the Class" (Turner's Syndrome)
"Timmy and the 'Big Kids'" (Constitutional Short Stature)
"Different From My Friends" (Turner's Syndrome and Delayed Puberty)

Themes:
Adolescent Health, Growth in Children and Adolescents

Key Words:

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Delayed puberty, puberty, growth disorders, pubertal development, sexual maturation, celiac disease, malabsorption, weight loss

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: Tanner Stages of Secondary Sexual Characteristics – Female
- Handout #2: Tanner Stages of Secondary Sexual Characteristics – Male
- Handout #3: Sarah's Growth Chart Before Treatment
- Handout #4: Sarah's Growth Chart After Treatment
- Bibliography

Facilitator Preparation:

Facilitators should thoroughly review this guide and the other materials provided. 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: Sarah is a 13 6/12 year-old patient with lack of weight gain, an attenuation of growth velocity, and arrested pubertal development. Fortunately, she has been followed by the same pediatrician since birth and there is clear documentation of past weight and growth points, as well as her general health, psychosocial development, and relationships with her family, school and community. Pubertal arrest in the face of poor weight gain should lead the primary care clinician to consider nutritional causes. In contrast, girls who are overweight for height and not growing normally often have an endocrine cause for the arrest. Utilizing both past growth data, as well as the current information obtained, assists the learner in formulating a differential diagnosis.

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

Sarah is a 13 6/12 year-old who comes to your office with slowed growth and delayed pubertal development. In response to your questions about her concerns, Sarah replies, *"My mother is worried because I haven't*

grown very much in the past year. She thinks my height and weight are the same, and I'm the only girl in my class who hasn't gotten my period." Sarah has been in good health with no chronic medical problems and no acute illnesses. She likes to eat and remarks that her appetite has increased over the past two years. She eats a good variety of foods with no restrictions. She is active in sports, playing soccer most days for about 2 hours. She denies abdominal pain, nausea, vomiting, bloating and diarrhea. Her bowel movements are formed and often hard every other day. She has had no skin, joint, or visual complaints. Your records show that one year ago, Sarah's breast and pubic hair development were both in Tanner stage 2.

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? To assess whether the patient's concerns regarding her growth and development are accurate, 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?

It is also important to assess other stressors, family constellation, intensity of sports participation, concerns about weight and nutritional intake, and how much communication she has had at home about her pubertal development. Questions from *Bright Futures* include:

- 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?

Sarah appears to be eating well although many girls with eating disorders may deny these behaviors. Her exercise level is not sufficient to likely be associated with pubertal delay.

Family history would also be important (*e.g.* history of short stature, history or miscarriages, age of pubertal onset in each parent, pubertal delay in other family members, etc). The heights of both parents should be determined in order to calculate 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 through *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.) Her history is particularly worrisome because she started pubertal development and then stopped, and she is not going through a growth spurt typical of early puberty.

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 developmental in 15-30% of girls; pubic hair development precedes breast development more commonly in African-American girls than in Caucasian girls. The breast and pubic hair maturation should be staged separately to allow for recognition of discrepancies of development. Remind learners that breast development is stimulated predominantly by ovarian estrogen secretion while pubic hair development is stimulated by secretion of adrenal androgenic hormones.

Distribute Handout #1: Tanner Stages of Secondary Sexual Characteristics – Female and Handout #2: Tanner Stages of Secondary Sexual Characteristics – Male. Allow a few minutes for learners to review the contents.

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 and extent of delayed puberty and growth deficiency. The growth spurt occurs during early adolescence in a girl, typically occurring between Tanner breast stage 2 and 3 with peak height velocity at 11.5 years. Menarche occurs at a mean age of 12.7 ± 1.0 years, about 2-2 ½ years after the onset of breast development and on the downslope of the height velocity curve.

What is your assessment of Sarah's pubertal development? 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. The average age with standard deviation (SD) for attainment of pubertal milestones in North American girls is age 10.9 ± 1.0 years for breast budding (Tanner 2) and 11.2 ± 1.1 years for pubic hair development (Tanner 2). Although concerns have been raised about the reproducibility of recording Tanner 2 breast development (which can be mistaken for fatty tissue in overweight girls), Herman-Giddons reported that the

mean age of breast development in African-American girls was 8.87 years and 9.96 years in white girls.[5] For pubic hair, the mean ages for development were 8.78 years and 10.51 years, respectively.

While our patient underwent thelarche (developed breast buds) at a normal time, her development has not continued to progress. The mean duration of complete pubertal development is 4.2 years in a girl (range of 1.5-6 years), and menarche typically occurs 2½ years after thelarche. Her past medical records reveal that her puberty has been completely *arrested* since the age of 11 years (when breast buds were noted).

Distribute Part II of the case along with Handout #3: Sarah's Growth Chart Before Treatment. Ask one or more learners to read it aloud.

Part II

Sarah's past medical history is unremarkable. She was a full-term gestational infant. She is on no medications and has had no operations or hospital admissions. She developed breast buds at age 11 years, followed by development of scant pubic hair.

Her mother's height is 64" and the father's height 69"; therefore, the patient's mid-parental height is ~64". Her mother had menarche at age 13.

On physical examination, she is a thin, but otherwise well-appearing adolescent girl.
Sarah's height is 62 ¼ inches and her weight is 84 pounds which you plot on her growth chart.

Vital signs: blood pressure 95/54, pulse 72.
Skin: clear, without comedones or other lesions.
HEENT: pupils rounds and equally reactive. Sclerae clear. Extraocular muscles intact. Oropharynx clear.
Neck: no goiter or lymphadenopathy.
Chest: Tanner 2 breast development. Lungs clear.
Heart: normal sinus rhythm, without murmur, gallop or rub.
Abd: soft, no hepatosplenomegaly or masses.
GU: Tanner 2 pubic hair. Normal external genitalia. Rectoabdominal exam revealed a small cervix and no adnexal masses. Stool - negative for occult blood.
Neuro: nonfocal, normal reflexes, without delayed relaxation.
Spine: no scoliosis

What specific parts of the physical examination/health assessment are particularly important? Would you perform a pelvic examination?

The most important parts of the assessment are a height, weight, determination of Body Mass Index (BMI), blood pressure, general physical examination and Tanner staging/sexual maturity rating.

In the girl with delayed puberty, an internal examination is not needed because the differential diagnosis is largely between a hypothalamic-pituitary cause (*e.g.* slowing of GnRH pulses from a systemic illness) or an ovarian cause. 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 in this patient particularly to check stool for occult blood, but it is an optional examination if stool samples can be obtained for testing. 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 for Sarah's pubertal delay? (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 residents 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

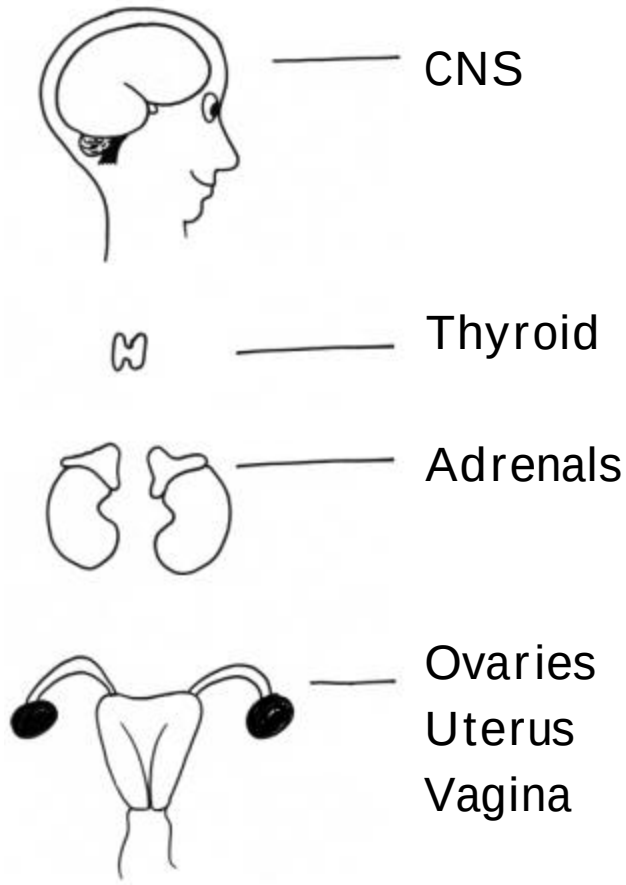
Ovaries:

- 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

Sarah has a process that has interrupted both weight gain and linear growth. Self-induced weight loss (e.g. anorexia nervosa) and systemic diseases (e.g. Crohn's disease, celiac disease) need to be considered. As the patient appeared to be previously healthy, the learner should

consider the processes that either develop in early to middle adolescence or that fail to manifest themselves during childhood.

Example Blackboard Drawing:



As a primary health care provider, 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 outlined. It is helpful to list all 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, and decide what a second and third step are. A screening CBC, ESR and chemistries should be obtained to exclude a chronic illness. Screening endocrine tests that are important include: a thyrotropin stimulating hormone (TSH) level (to exclude hypothyroidism) and a follicle stimulating hormone (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 (T_4, TBGI) should be obtained. Prolactin level is drawn if the FSH level is low; karyotype and other studies to determine the etiology of ovarian

failure if the FSH level is high. A hand and wrist radiograph for determination of bone age helps to estimate final height and to ascertain if bone age is delayed more than height age (common with hypothyroidism). Given the fall-off in weight before height, a screening test for celiac disease should be discussed.

CBC - HCT 34% with MCV of 74 (mild microcytic anemia; other indices within normal limits), normal WBC and platelets
Sedimentation rate (ESR) Liver function tests, electrolytes, BUN, creatinine, glucose, albumin, total protein, Ca, phosphorus - NORMAL
Bone age (chronologic age 13 years) = 12 years (one standard deviation is 10 months)
Slightly DELAYED
Thyroid function tests: T4 8.6 µg/dl, TSH 1.8 µU/ml, TBGI 0.95
NORMAL
FSH 2.3 IU/L -NORMAL
Endomysial Antibodies: markedly elevated titers (POSITIVE - consistent with celiac disease)

What do you know about celiac disease? The endomysial antibody titer has yielded the critical information and the laboratory investigations are consistent with celiac disease.

Celiac disease (also know as celiac sprue, gluten-induced enteropathy, or nontropical sprue) is an intolerance of the protein gluten found in wheat and rye. The damage to the intestinal mucosal tissue is caused by a toxic reaction to the gliadin fraction of gluten. Two theories exist as to the disease's pathogenesis: (1) the mucosal lesion of celiac disease is due to an inborn mucosal enzyme defect which permits undigested toxic compounds to accumulate in the mucosal wall; (2) the intestinal damage is secondary to immune reactions to the "antigen" gliadin. A diffuse lesion of the upper small intestinal mucosa is seen with short, flat villi, deepened crypts, and irregular vacuolated surface epithelium with epithelial lymphocytes. Clinical manifestations range from severe malabsorption to normal or near normal health. As was seen in this patient, the most constant features are decreased rates of weight gain and linear growth, which may persist without gastrointestinal symptoms. Some patients with celiac disease remain well during childhood with the disease not manifesting until adulthood. Diagnosis is based on a finding of serum endomysial and/or gliadin antibodies; the finding of the characteristic duodenal or jejunal mucosal lesion on a mucosal suction biopsy; and/or a clinical response to a gluten-free diet. With the advent of a sensitive anti-endomysial, anti-gliadin and other antibody screening assays (e.g. transglutaminase antibody), the need for definitive intestinal biopsies may have declined.

Distribute the Epilogue, Handout #4: Sarah's Growth Chart After Treatment, and Bibliography. Ask someone to read the Epilogue aloud.

Epilogue

Sarah is currently age 14 6/12 years. She was begun on a gluten-free diet once the diagnosis of celiac disease was made. She has shown a good response to therapy with a marked acceleration of her growth velocity. Her breast and pubic hair development resumed within 6 months of initiation of this modified diet, and she just experienced menarche.

She is a good student, has many friends and has adjusted well overall to the dietary restrictions under which she has been placed. She is pleased with the clinical response of the regimen, continuous compliance with this strict diet is not an easy task, particularly for a teenager, and she requires close medical follow-up.

Discuss the management plan for this patient.

Nutritional issues: A gluten-free diet is the mainstay of therapy for patients with celiac disease. Eighty-percent of patients respond to this dietary intervention. Symptomatic improvement typically occurs within a few weeks, and tests of absorptive function and small-bowel histologic changes improve typically after a few months.

Growth: Normal growth velocity will likely resume after this patient is placed on an appropriate nutritional regimen. This is accomplished by initiation of a gluten-free diet.

Sex hormone replacement: Sex steroid replacement (estrogen) is not needed in this case because normal GnRH and accompanying LH and FSH secretion will resume after the patient's nutritional status improves.

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 Celiac Disease, as well as other areas of 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. Invite a nutritionist to come and talk about a gluten-free diet.
2. Visit a school and ask how special meals can be accommodated.
3. Find out how to access services from the National School Lunch Program.
4. Check out web sites on Celiac Disease and see which ones might be appropriate for teens, parents, and/or medical providers.

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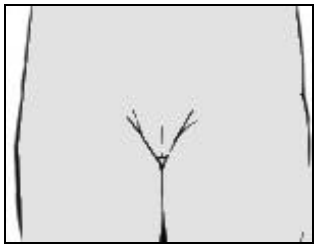
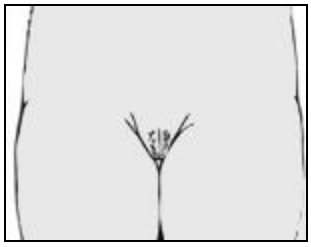
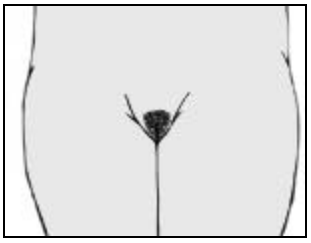
Will I Ever Get My Period?
Handout #1: Tanner Stages of Secondary Sexual Characteristics—Female



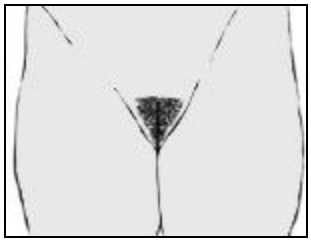
Stage 1



Stage 2



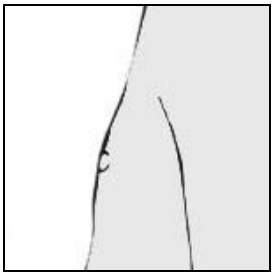
Stage 3



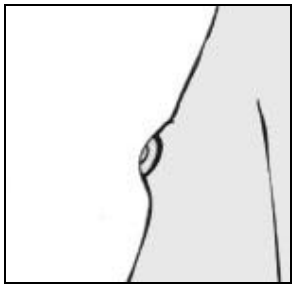
Stage 4

Stage 5

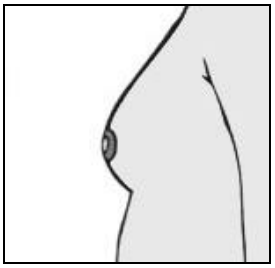
<u>Female pubic hair development</u>. *Tanner stage 1*: Prepubertal, with no pubic hair. *Tanner stage 2*: Straight hair is extending along the labia, and between rating 2 and 3, begins on the pubis. *Tanner stage 3*: Pubic hair has increased in quantity, is darker, and is present in the typical female 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.



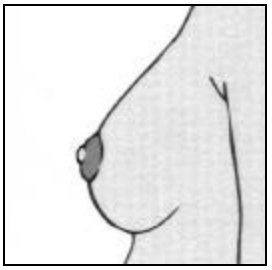
Stage 1



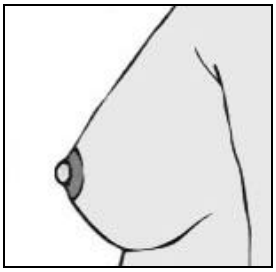
Stage 2



Stage 3



Stage 4



Stage 5

<u>Female breast development</u>. *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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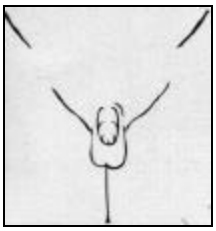
Handout #2: Tanner Stages of Secondary Sexual Characteristics--Male


Stage 1


Stage 2


Stage 3


Stage 4


Stage 5

Male pubic hair development: *Tanner stage 1:* Prepubertal, with no pubic hair. *Tanner stage 2:* Sparse growth of long slightly pigmented downy hair, straight or only slightly curled, at base of penis. *Tanner stage 3:* Hair is darker and more curled and spreads sparsely over junction of pubes. *Tanner stage 4:* Hair is adult in type and covers an area smaller than most adults. *Tanner stage 5:* Adult quantity and pattern of pubic hair, with hair present along the inner borders of the thighs.

Male genital development: *Tanner stage 1:* Prepubertal. *Tanner stage 2:* Scrotum and testes have enlarged and the scrotal skin becomes more textured. *Tanner stage 3*: Growth of the penis has occurred, especially in length. Testes and scrotum are further enlarged. *Tanner stage 4:* The penis is further enlarged in length and breadth. Glands has become larger and broader. Scrotum is darker. *Tanner stage 5:* The testes and scrotum are adult in their size.

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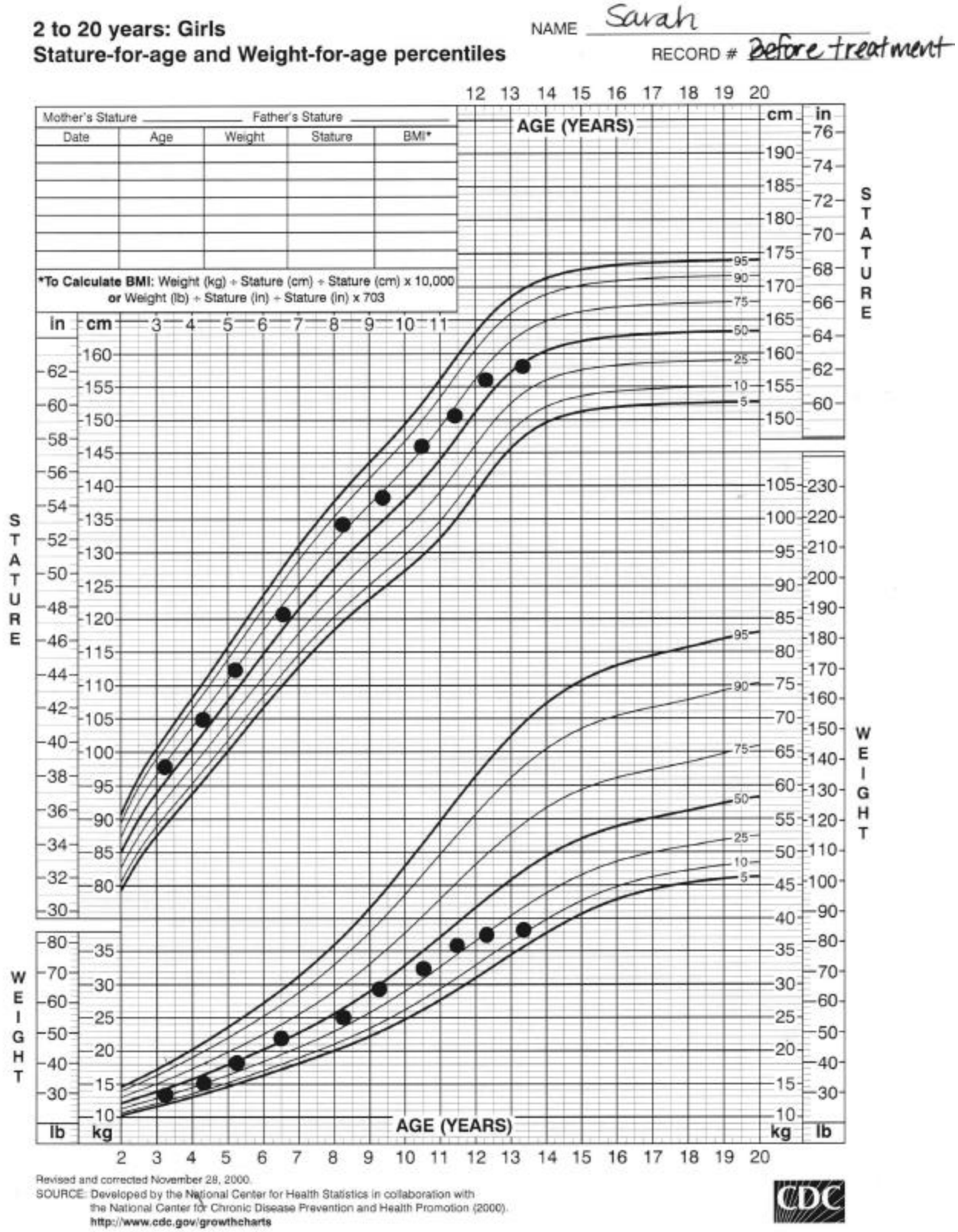
Handout #3: Sarah's Growth Chart Before Treatment



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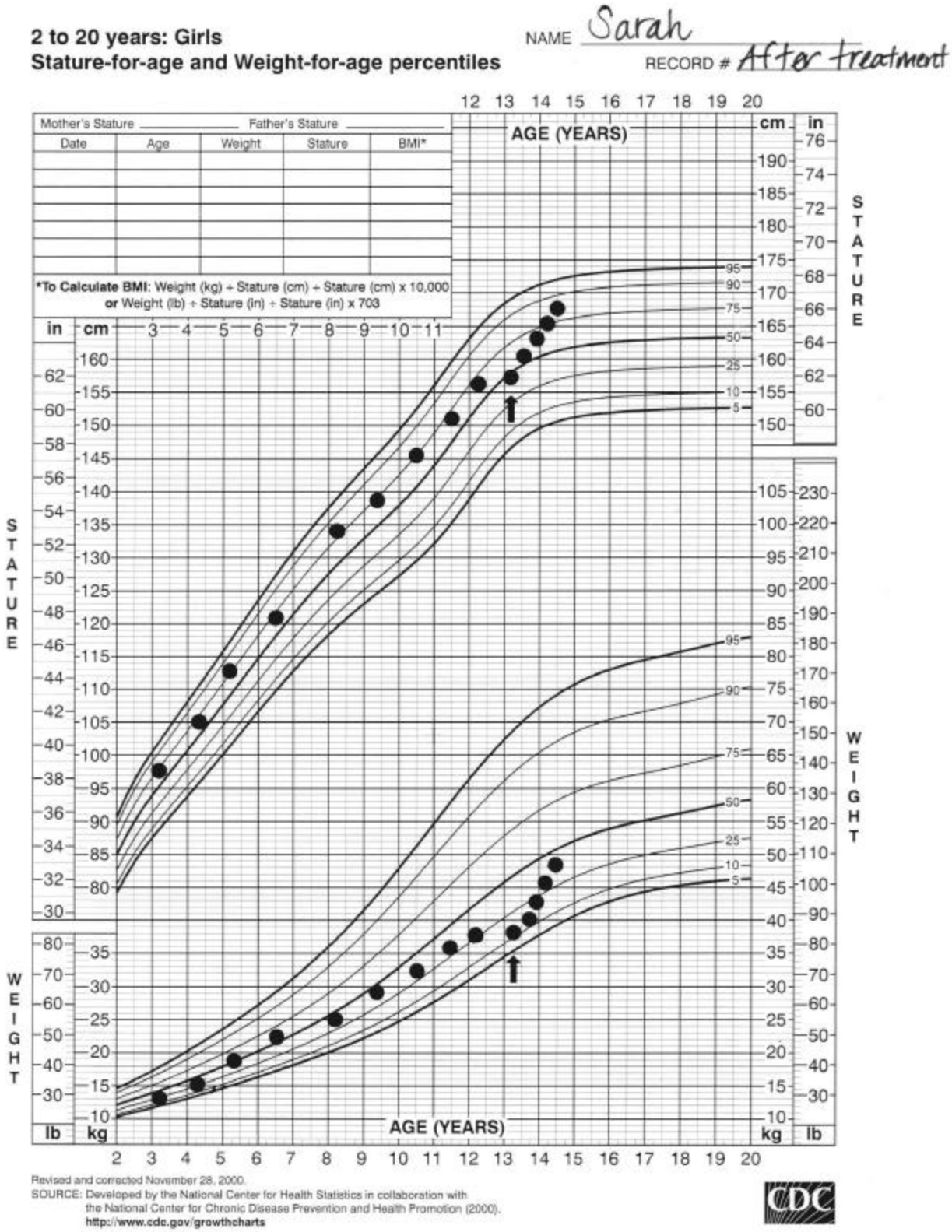
Handout #4: Sarah's Growth Chart After Treatment



*****Arrow (⬆) indicates the initiation of the Gluten-free diet.*

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3. Emans SJ, Laufer MR, Goldstein DP. *Pediatric and Adolescent Gynecology*, fourth edition. Philadelphia: Lippincott, Williams and Wilkins; 1998.
4. Frick TJ, Olsen WA. Celiac disease and the spectrum of gluten sensitivity. *Gastroenterologist* 1994;2:285-92.
5. Herman-Giddens ME, Harlan EA, Grillo GP et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research of Office Settings Network. *Pediatrics* 1997:99(4):505-12.
6. Troncone R, Greco L, Auricchio S. Gluten-sensitive enteropathy. *Pediatric Clinics of North America* 1996;43:355-76.

Suggested Reading (Annotated)

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.

Herman-Giddens ME, Harlan EA, Grillo GP et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research of Office Settings Network. *Pediatrics* 1997:99(4):505-12.
This article provides ages of pubertal development in white and black U.S. girls from a PROS study based in office practice.

Troncone R, Greco L, Auricchio S. Gluten-sensitive enteropathy. *Pediatric Clinics of North America* 1996;43:355-76.
An overview of the pathophysiology, diagnosis and management of celiac disease.

Educational Resources on the World Wide Web

http://www.naspgn.org/disease_information.htm This is the official site for the North American Society for Pediatric Gastroenterology and Nutrition which provides an easy-to-follow informational guide for children and families with Celiac disease.