Breast Development

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The difference between humans and other mammals is that we know how to accessorize.

—Madeline Albright

Learning Objectives:
1. Develop a plan for the evaluation and management of adolescents and young adults presenting with breast complaints.
2. Discuss differential diagnosis of abnormalities in breast development.
3. Distinguish between idiopathic and pathologic gynecomastia in adolescent males.

Primary Reference:
https://pedsinreview.aappublications.org/content/28/9/e57

CASE ONE:
You are seeing Olive, a 14-year-old girl, in the office for a routine well child visit. She has no medical conditions and has been generally healthy. When asked about specific concerns, she points to her breasts and states that they look “lopsided”. She wears baggy clothes to cover her chest and has been hesitant to participate in sports fearing that her peers will make fun of her. She denies any masses, nipple discharge, pain or discoloration. Looking back in the chart, you note that you documented thelarche at 8 years.

1. Describe breast development in a female, including hormonal influences, staging, and expected timeline.

Estrogen promotes the growth of fibroadipose tissue and lactiferous ducts, whereas progesterone stimulates lobular tissue and development of alveolar budding. The Pediatric Research in Office Setting Network studies reveal that breast development in girls is occurring at an earlier age than previously suggested. Multiple studies have concluded that the lower age limit for thelarche may differ based on BMI and ethnic/race differences. The new acceptable lower age limit for thelarche in African-American girls is 6 years of age (with average age of 9.5 years), and in Caucasian girls, 7 years (with average age of 10.3 years). Though referral to an endocrinologist for breast development before 8 years of age is reasonable, further evaluation may not reveal any true pathology. The reasons for shifting norms, including differences based on ethnicity and race, are unclear. Ongoing research shows correlation of earlier pubertal onset with exposure to environmental chemicals such as bisphenol A, as well as with the rise in childhood obesity.

Thelarche is considered delayed if there is no evidence of breast development by age 13. Full breast development takes about 4.2 years on average. Based on her history and reassuring physical exam, this patient has normal breast development. The classification of breast development in females is best described by sexual maturity rating (SMR) (i.e., Tanner Stages). Moderators can review sexual maturity rating as pertains to breast development (see Resources).

2. How and when should one perform a breast examination for children and adolescents?

Breast examination should be a part of the routine physical examination in females and males. For younger children and at most health supervision visits, the exam involves brief inspection and palpation to assess for SMR. Data and guidelines are lacking to support a more comprehensive screening clinical breast exam (CBE) for adolescents, but if specific complaints (e.g., masses, mastalgia, nipple discharge) are reported, or abnormalities are found on the brief exam, then CBE should be performed. A breast
evaluation allows clinicians to assess concerns raised by the patient and reassure patients that their breasts are growing and developing appropriately. In addition, it may reveal breast anomalies such as asymmetry, hypertrophy, nipple abnormalities, masses, and other breast concerns that adolescents may feel too self-conscious to disclose to their providers.

The first step of CBE is inspection during which the patient is in the upright position. Size, symmetry, dimpling, nipple, color changes and SMR are noted. The second step, palpation, is performed while the patient is in the supine position with one arm over the head. With the flat finger pads, the breast tissue is examined using either the vertical strip method, concentric circular, or the clockwise method. The subareolar tissue is gently compressed and milked toward the nipple in order to detect discharge. Lastly, clinicians should also palpate the axillary, supraclavicular, and infraclavicular lymph nodes.

3. What is the most likely diagnosis in this patient? What are some other disorders of breast development?

Normal development of the breast may be disrupted from various conditions and result in abnormal features in terms of size, symmetry, number, and nipple morphology. Prompt evaluation and appropriate referral may help reduce anxiety in adolescent and/or family surrounding breast concerns.

The most likely diagnosis in this case is breast asymmetry which is one of the most common breast complaints among adolescents. It is usually most pronounced when the breasts are developing and may be due to hormonal fluctuation and end organ sensitivity. Insults to the prepubertal breast such as trauma and infection may also lead to asymmetry. While asymmetry tends to improve during the later years of development, there may still be some normal variant degree of asymmetry through adulthood.

An exam including measurement of the areola, glandular breast tissue (upper-to-lower or right-to-left) and overall breast size should be performed to exclude pathological causes of asymmetry. Until they reach breast maturity, adolescents may opt to wear padded bras or prosthetic inserts to mask the asymmetry. Surgical intervention should be deferred in the setting of a normal evaluation coupled with lack of psychosocial impairment, until the breasts are fully developed, usually after 17-18 years old.

Clinicians should be aware that breast asymmetry is not just a cosmetic issue as it has been shown to lower self-esteem in adolescent girls, and should provide recognition of the impact that breast asymmetry can have on an adolescent and appropriate psychological and emotional support in an empathetic forum where the adolescent can express their concerns.

Polymastia (supernumerary breast tissue) and polythelia (accessory nipples) are quite common and may be seen anywhere along the embryonic milk line. Surgical excision of the accessory tissue may be warranted to prevent pain secondary to hormonal changes, specifically during pregnancy and for cosmetic needs. Amastia, the absence of breast glandular tissue, and athelia, the absence of areolar tissue, may be associated with other chest wall anomalies such as Poland Syndrome, which consists of the underdevelopment or absence of the pectoralis muscle on one side of the body. Unilateral hypomastia may occur after radiation therapy to the chest wall, thoracostomy, or placement of central lines, while bilateral involvement could indicate ovarian pathology, hypothyroidism, or androgen producing tumors. However, if small breasts are associated with normal pubertal development, no further workup is warranted and reassurance should be provided.

Juvenile breast hypertrophy is the uncontrolled spontaneous growth of the breast occurring shortly after thelarche. It is a rare occurrence during the adolescent period and is thought to be due to excessive end-organ sensitivity to gonadal hormones. Association with an autoimmune process has been suggested, as it has been found in patients with rheumatoid arthritis, Hashimoto’s thyroiditis, and myasthenia gravis. Symptoms may include back or shoulder pain given the excessive weight of the breasts. Treatment depends on the stage of the patient’s growth. During the initial phase of breast development, medications with anti-estrogenic effects such as Tamoxifen or progesterone may be used to control growth. Concurrent use of a supportive bra may also relieve back pain. Once patients have reached full breast development, mammoplasty reduction is considered for cosmesis and pain relief.

Tuberous breasts are a variant of breast development resulting in underdeveloped nipples and areola. They share the following common features: hypoplasia, elevated inframammary fold, narrow breast base, and glandular herniation through the areola. While the etiology remains unclear, some patients with a
history of gonadal dysgenesis or ovarian insufficiency have developed tuberous breasts following exposure to higher doses of exogenous hormones. Conservative treatment with close follow-up and supportive reassurance is recommended, but surgical options are often desired by the affected patient.

CASE TWO:

Bluto is a 16-year-old male presenting for a sports physical examination. He has no major concerns and cardiovascular screening questions are all negative. He states that he has been under a lot of pressure and wants to make his family and friends proud by taking his team to championship this year. As you proceed to do a cardiopulmonary exam, you notice enlarged breast tissue bilaterally.

4. How would you further evaluate this patient? What is the most common cause of breast enlargement in the age group?

Teenage males are usually reluctant to disclose their concerns regarding breast enlargement and those affected may experience severe embarrassment and emotional distress. About two-thirds of adolescent males will develop physiologic gynecomastia, the proliferation of glandular breast tissue, during puberty, with peak onset around 13 to 14 years of age, typically regressing within a year. Physiologic gynecomastia likely results from an imbalance of estrogen and androgen as maturation of testosterone secretion lags allowing for increased estrogenic effect, or increased sensitivity of tissues to normal estrogen levels. This should be distinguished from pseudogynecomastia, which is an enlargement of adipose breast tissue, and from pathologic gynecomastia.

Elements of a history for evaluation of breast enlargement should include age of onset of gynecomastia, progression, tenderness/pain, nipple discharge, surgery for cryptorchidism or hypospadias, drug use, topical products and environmental exposures.

Observation of the breasts is completed by having the patient sit upright with hands hanging on the sides. Then, with the patient lying down with hands placed behind the neck, palpate the breast and nipple shape/contour. The diameter should be documented as breasts with larger diameter >4 cm may indicate an underlying pathological etiology. Exam findings usually involve a round mobile subareolar mass, which may be unilateral, bilateral and/or asymmetrical. In addition, documentation of body habitus, liver size, testicular volume and consistency (small firm testes could be consistent with Klinefelter syndrome), and neurologic status further elucidates important etiological information.

5. What are the different causes of non-physiologic gynecomastia? What additional information should be obtained in support of the presumed clinical diagnosis?

Non-physiologic (pathological) gynecomastia is rare in adolescents and prepubertal boys. The etiology may stem from endocrinopathies, enzymatic defects, systemic disease, medications, and drugs of abuse. The differential diagnosis and associated mechanisms are listed below in Table 1.

<table>
<thead>
<tr>
<th>Diagnosis &amp; examples</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td><strong>Endocrine</strong></td>
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<tr>
<td>1º Hypogonadism (e.g., Klinefelter syndrome, testicular torsion, testicular trauma, orchitis, 5alpha reductase deficiency)</td>
<td>Testicular dysfunction decreasing serum testosterone and abnormally elevated LH promoting aromatization of testosterone to estradiol which results imbalance estrogen and testosterone</td>
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<tr>
<td>2º Hypogonadism (e.g., Kallman Syndrome, hyperprolactinemia-rare)</td>
<td>Decreased LH with low estrogen and testosterone; Abnormal estrogen-to-testosterone ratio</td>
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<tr>
<td>Hyperthyroidism (e.g., thyrotoxicosis)</td>
<td>Aromatization of elevated level of androstenedione</td>
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<td>Congenital Adrenal Hyperplasia</td>
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<tr>
<td>Androgen resistance syndrome</td>
<td>Absence of androgen receptor in androgen target tissue</td>
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<tr>
<td>Diagnosis &amp; examples</td>
<td>Mechanism</td>
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<tr>
<td><strong>Tumors</strong></td>
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<td>Testicular (e.g., Germ cell tumor, Leydig cell tumor)</td>
<td>Secretion of hCG resulting in high level of estradiol compared to testosterone by the testis (germ cell tumor)</td>
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<tr>
<td></td>
<td>Secretion of estradiol (Leydig cell tumor)</td>
</tr>
<tr>
<td>Liver (e.g., Hepatocellular carcinoma)/ Adrenal</td>
<td>Increased aromatization of androgen precursors to estradiol</td>
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<td><strong>Systemic Illnesses</strong></td>
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<tr>
<td>Chronic Kidney Disease</td>
<td>Destruction of testis and suppression of testosterone due to uremia</td>
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<tr>
<td>Chronic Liver Disease</td>
<td>Impaired estrogen catabolism and increased SHBG resulting in increased peripheral estrogens</td>
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<td></td>
<td>Presence of phytoestrogens in ethanol; inhibited production of testosterone by ethanol</td>
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<tr>
<td>Malnutrition and refeeding</td>
<td>Recovery from weight loss leads to transient decrease in estrogen catabolism and abnormal ratio of estradiol-to-testosterone</td>
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<tr>
<td><strong>Medication/drug-related</strong></td>
<td></td>
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<tr>
<td>Topical estrogen, phytoestrogen, hCG, anabolic steroid</td>
<td>Increased serum estrogen</td>
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<tr>
<td>Ketoconazole, metronidazole, alkylating agents, anabolic steroid</td>
<td>Inhibition of testosterone synthesis</td>
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<tr>
<td>Spironolactone, cimetidine, flutamide, cannabis</td>
<td>Androgen receptor antagonism</td>
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<tr>
<td>Antipsychotic agents (haloperidol, phenothiazine), metoclopramide, verapamil</td>
<td>Increased serum prolactin</td>
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<tr>
<td>tricyclic antidepressants, selective serotonin reuptake inhibitors, highly active antiviral therapy, isoniazid, protein pump inhibitor</td>
<td>Unclear mechanism</td>
</tr>
</tbody>
</table>

A stepwise approach with laboratory testing including a complete metabolic panel with liver enzymes and TSH should be implemented in the evaluation of patients with probable non-physiologic gynecomastia. Additional labs such as fasting total and bioavailable testosterone, estradiol, LH, and FSH can be helpful in suspected hypogonadism; beta-hCG and DHEAS can also rule out testicular or adrenal tumors. Imaging studies are not recommended though testicular ultrasonography can be obtained if palpable testicular mass is noted on exam.

6. **How would you manage patients with gynecomastia? When should you refer?**

Management of gynecomastia is directed toward the underlying cause: weight loss for pseudogynecomastia; discontinuation of the causative agent for drug induced gynecomastia; treatment of underlying endocrinopathies and systemic illnesses. The mainstay treatment of physiological gynecomastia is close follow up and reassurance. It is important to emphasize that these are not growing breasts and that the boy does not have cancer. Studies have demonstrated breast size reduction in adolescents with the use of tamoxifen and raloxifene. However, data remains limited as these studies are uncontrolled with small sample size. Surgical correction may be an option in persistent gynecomastia (>2 years of physiologic gynecomastia) if associated with psychological distress. Patients with underlying pathological conditions, macrogynecomastia (>4 cm), unresolved non-drug induced galactorrhea, or bloody nipple discharge should be referred to a pediatric endocrinologist.

**Additional References:**

Resources:
1. Sexual Maturity Rating (Tanner Stages).
2. General information about breast health for young women.
   https://youngwomenshealth.org/2014/02/27/breast-health/
3. Handout about common breast concerns.