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## Breast Disorders in Children and Adolescents

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*Chapter 6*

## **BREAST DISORDERS IN CHILDREN AND ADOLESCENTS**

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Concerns about problems of the breast are often noted in adolescents and their parents. This review discusses issues and disorders of the breast in children and adolescents, starting with basic principles of embryology and adolescent breast development. Concepts that are covered include congenital breast disorders, abnormal timing of breast development, breast asymmetry, underdeveloped breasts, breast atrophy, tuberous breasts, mammary hyperplasia, fibroadenoma, giant fibroadenoma, cystosarcoma phyllodes, intraductal breast papilloma, adenocarcinoma, mastitis, traumatic breast disorders, benign breast disease, fibrocystic change, mastalgia, gynecomastia, and galactorrhea. A number of figures are provided illustrating breast pathology. Clinicians caring for children and adolescents are encouraged to provide careful assessments of this important organ system.

## INTRODUCTION

The breast is a modified sweat gland enveloped by superficial thoracic fascial layers and suspended from the chest wall by Cooper's ligaments (fibrous septae), extending from the pectoralis fascia to the dermis (1,2). Breast concerns and disorders are an often ignored part of health care, sometimes neglected by the clinician, and typically worried about by the child or adolescent. Parents may be anxious about perceived breast problems in their child while the adolescent may present with unexpressed concerns about this body system. Body image and self esteem issues in girls may be strongly associated with breast appearance and breast development during the adolescent years. Breasts (mammary glands) are estrogen-dependent organs that indicate sex development, functional activity of ovary, and development of reproductive function. Diagnosis and treatment of breast disorders are important tasks for clinicians who care for children and adolescents (3-5). Examination of the breasts may occur as part of a comprehensive physical examination or because anxiety is raised about a possible problem. This review presents common concerns and problems of the breast that may arise in children and adolescents (6-8).

## EMBRYOLOGY

During the 4th to the 6th fetal week, epidermal cells migrate into underlying mesenchyme, resulting in the development of primitive mammary ridges or milk lines (9). Ectodermal thickening occurs from the axilla to the groin. Atrophy of the upper and lower parts of these ridges usually occurs around the 10th fetal week, allowing the middle or pectoral ridges to eventually become normal breast tissue. Lactiferous duct and mammary glands later develop from these ridges, while the surrounding mesenchyme becomes fibrous and adipose tissue within the breast. Solid cords, usually 15 to 20 in number, result from secondary buds in the breast tissue; these cords later become milk ducts and lobes of the breasts. The areola develops in the 5th month of fetal life and the nipple is normally seen shortly after birth.

## NORMAL ADOLESCENT BREAST DEVELOPMENT

Childhood breasts are composed of ducts that are lined with epithelium and surrounded by connective tissue; the child's breast tissue usually is dormant until puberty ensues (9). As puberty develops, female breasts change due to the increase of the hormones estrogen, progesterone, and eventually, prolactin. However, during premature (isolated) thelarche/premature breast development, the level of estrogen is not increased. Some researchers believe that testosterone could have specific influence for breast development, but this opinion is still controversial (10). For example, absence of suppressive effects of testosterone for breast development in girls with a low estrogen level who are not sensitive to androgen, could lead to normal size breasts, as in the case of androgen insensitivity syndrome (testicular feminization syndrome). Perhaps breasts develop under increasing estradiol secretion by testicles and peripheral aromatization of testosterone (10). Other hormones needed for normal breast growth include thyroxine, insulin, growth hormone, and adrenal corticosteroids. Deficiency in one or more of these hormones can result in defects of the breast organ.

At first in early puberty, there is an increase in adipose tissue along with initial growth of ductal and stromal tissue because of the effects of estrogen; increase in pigmentation and size of the areola are also due to estrogen effects. The increase in progesterone leads to alveolar budding, lobular growth, and secretory growth of lobules and alveoli; however, true alveoli only appear during pregnancy (11).

The growth of female breasts is divided into five stages, classically called Tanner Stages or Sexually Maturity Stages (SMR) (see figure 1) (12). The SMR stages of Tanner from 1962 were based on classic work of Reynolds and Wines in 1948 that was itself based on earlier work of Stratz in 1909 (1,2). There is no breast development in stage 1, the classic breast bud is stage 2, the small breast appearance is stage 3, the double-contoured appearance is stage 4 (due to the areola/nipple complex forming one mound on top of the breast tissue mound), and the single contour appearance with the nipple forming a little round edge on the top, is stage 5 (fully mature breast). Some adolescent females may not develop a stage 5 breast and may have the stage 4 appearance throughout adulthood. Persistence of stage 4 in adult life does not pose problems in general, though special advice and preparation is needed for lactation.

A number of clinical correlations are noted with the SMR stages (see table 1). Alveolar cells change into secretory cells, with full maturation developing later with the production of prolactin inducing alveoli that are lined with milk secreting cells. Edema fluid can increase in size by 50% during the luteal phase of the cycle and these females could eventually develop symptoms of premenstrual tension (PMT)/premenstrual syndrome (PMS) that include breast tenderness and swelling.

The mature breast can increase two to three times in size due to pregnancy, from the second month of pregnancy, under the influence of estrogen and progesterone produced by the placenta, and also lactation. The breasts start to enlarge due to increased fat deposition and glandular proliferation with potential doubling of the breast blood flow. Breast anatomy is shown in figures 2-4 (13,14). There are 15-20 lobes, consisting of 20-40 lobules which include 10-100 alveoli. The areola contains numerous Montgomery (sebaceous) glands (11).

**Table I. Clinical correlations with Tanner Stages\***

<b>Clinical features</b>	<b>Tanner stage</b>
Hematocrit rise in males	II-V
Alkaline phosphatase peak	II in female, III in male
Rise in serum uric acid levels (male)	II-IV
Mild regression of virginal hypertrophy (of breast)	V
Different counseling about concern for breast size	II or V
Appearance of menarche	Late III or IV
Appearance of "normal" gynecomastia (males)	II or III
Use of contraceptives	IV
Use of diaphragm	IV or V
Neisseria gonorrhoeae infection	
Vaginitis	I
Cervicitis	II+
Timing of breast reduction or rhinoplasty	V
Short male with growth potential	II
Short male with limited growth potential	IV
Appearance of acne vulgaris	II or III
Decreased incidence of serous otitis media	Post-II or III
Development of orthopedic disorders (Osgood-Schlatter disease, slipped capital femoral epiphysis, significant worsening of scoliosis)	II-III (II-IV for scoliosis)
Strong suspicion of organic disease	Regression of stages or unusual delay in stage progression

\*Used with permission from: Greydanus DE, Parks D, Farrell E. Disorders of the breasts in children and adolescents. *Pediatr Clin North Am* 1989;36:601-38



Figure 1. Tanner Stages or Sexually Maturity Rating Stages (SMR).

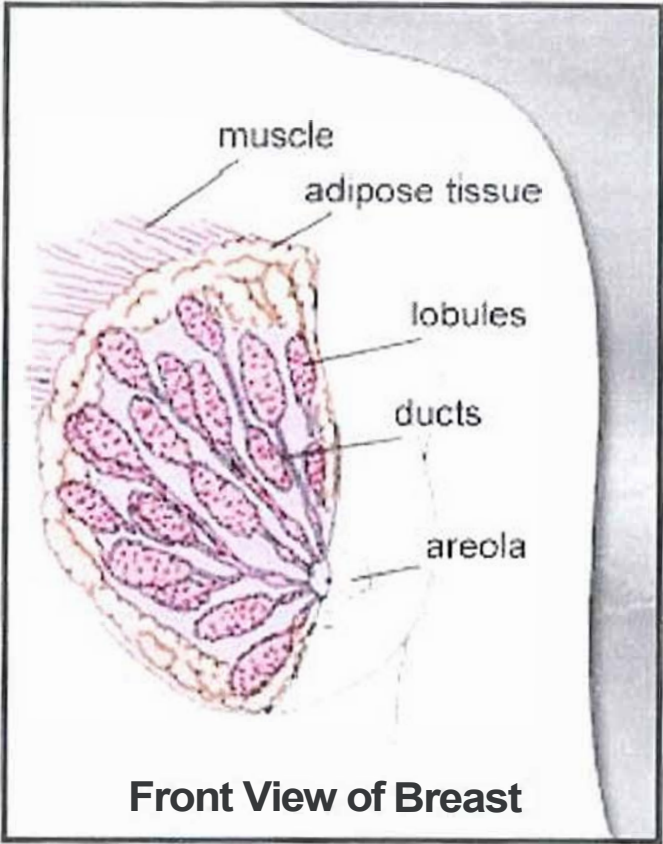


Figure 2. Breast Anatomy.



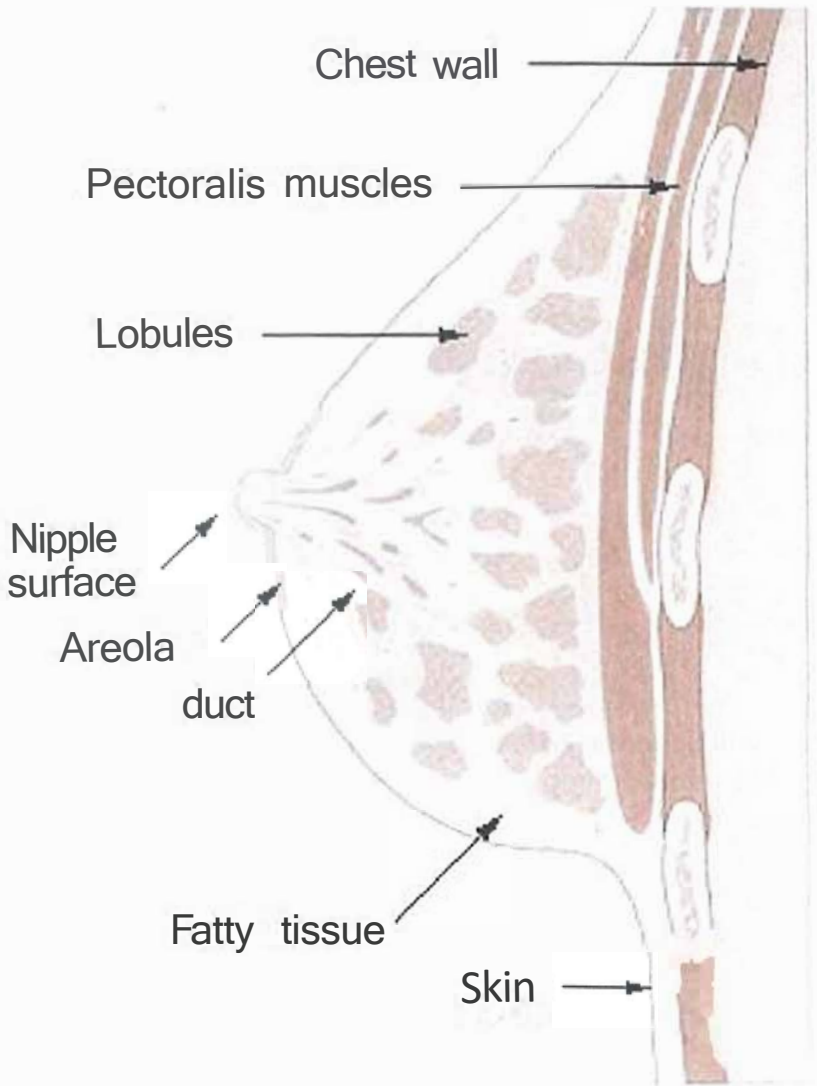


Figure 3. Breast Anatomy.

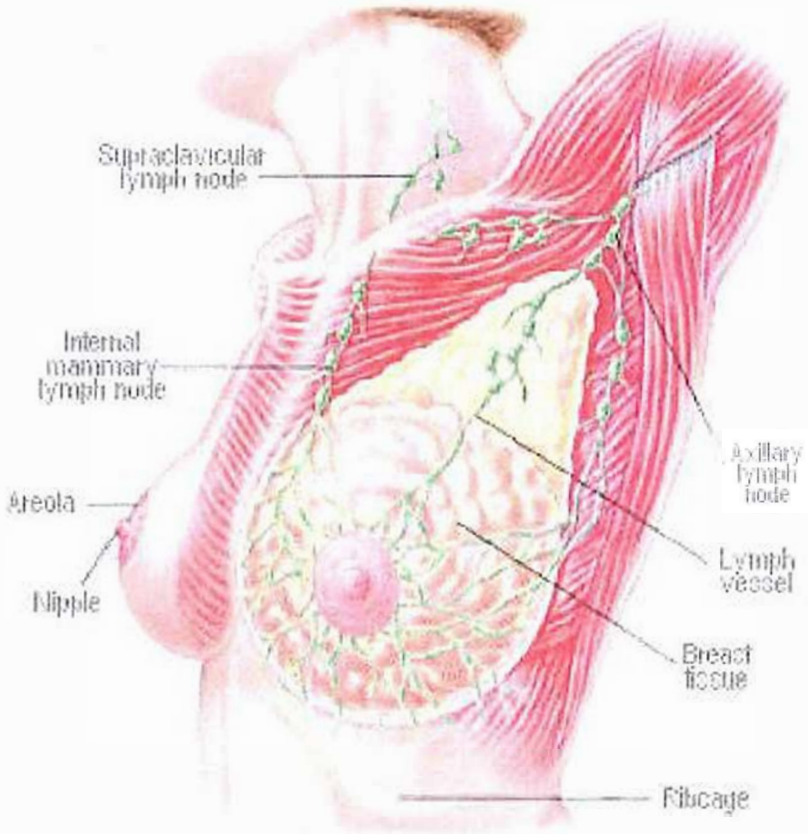


Figure 4. Breast Anatomy.

## BREAST EXAMINATION

### Self-examination

Many clinicians would not recommend routine self-breast examinations in adolescent females (except in those with a family or personal history of breast cancer), since breast malignancy is rare in this age group and it may produce increased psychological distress searching for such a rare condition; also, adolescents often do not exam themselves routinely for various reasons including limited knowledge of their bodies and busy life

activities that block their attention for such a recommendation. Arguments for encouraging youth to start breast exams is that it prepares them for such self-examinations as adults and that it is an effective way to find breast pathology.

## Clinicians' examinations

A number of methods for breast examination have been described and can be applied depending on the purpose of the examination (4,14). The male clinician may perform a limited exam, because of his own anxiety, concern over the patient's reaction to a breast exam, or out of a belief that no pathology is present in an adolescent. The male clinician may feel more comfortable with a chaperone in the room during the breast examination, as typically occurring during a pelvic examination (4). It is important to assess if the patient has any concerns about her breasts—such as being too small, too large, asymmetrical, or other. The exam can be used to provide often needed education about this important part of her body and its implications for current and future sexuality.

The adolescent should be taught that there is considerable amount of normal variation of breast size, shape, and consistency. Nipple size may also be quite varied. Swelling or enlargement may be noted along the outer lateral breast tissue curve extending into the axilla; this "axillary tail of Spence" is normal and can enlarge during puberty and pregnancy. There is also a normal variation in areolar hair, especially in some ethnic groups; however, this can be the first symptom of hyperandrogenemia and hirsutism (15,16). Plucking these hairs can lead to ingrown hairs and infection. If these hairs are bothersome, they can be cut short. A normal finding is a variable amount of areolar gland discharge and this should not be confused with galactorrhea. Also, the areola contains Montgomery tubercles that may temporarily secrete a whitish discharge under the stimulation of puberty, pregnancy, or lactation; it is not a disorder, is transient, and the only treatment is simple reassurance of its normalcy.

A number of tests have been used to delineate breast pathology. Masses may be evaluated with fine-needle aspiration (FNA), core-needle biopsy (CNB), or excisional biopsy (4,17, 18). A mammogram is usually not very helpful in adolescent females, because of the breast denseness

(i.e., increased fibroglandular to fatty tissue ratio) and also if the breasts are small (19). Ultrasonography is more effective at delineating masses within the immature breast (4,18,20). Color Doppler ultrasonography may increase the specificity of the diagnosis; cysts are avascular, fibroadenomas are hypovascular, and abscesses show increased peripheral flow (21). Computerized tomography (CT) may be necessary to locate a lesion in the breast tissue versus chest wall or other structures. The combination of palpation, imaging, and biopsy (FNA or CNB) is called the "triple test" of breast lesion evaluation (17,22).

## CONGENITAL ANOMALIES

### Nipple anomalies

A number of breast congenital anomalies can be seen, as noted in table 2. Polythelia or extra nipples, is described in 1% to 2% of the general population, and may be associated with other anomalies, such as genitourinary or cardiovascular defects (see figures 5,6) (9,14). These accessory nipples can be located anywhere along the milk lines, from the axilla to the groin (see figure 7); other sites have been noted as well, such as over the back or buttock (4). The nipple and areola of the accessory tissue is usually smaller than a normal nipple and may be mistaken for a mole, melanoma, or hemangioma (see figure 8). Excision of the extra nipple (s) is the typical management if the patient requests a cosmetic removal.

**Table 2. Congenital anomalies of the breast**

Polythelia
Athelia
Inverted nipples
Bifid nipple
Depressed nipple
Polymastia
Symmastia
Amastia
Poland syndrome



Figure 5. Congenital anomalies: two nipples (right breast) in a 14 year old girl. Mole is seen at the medial aspect of right breast

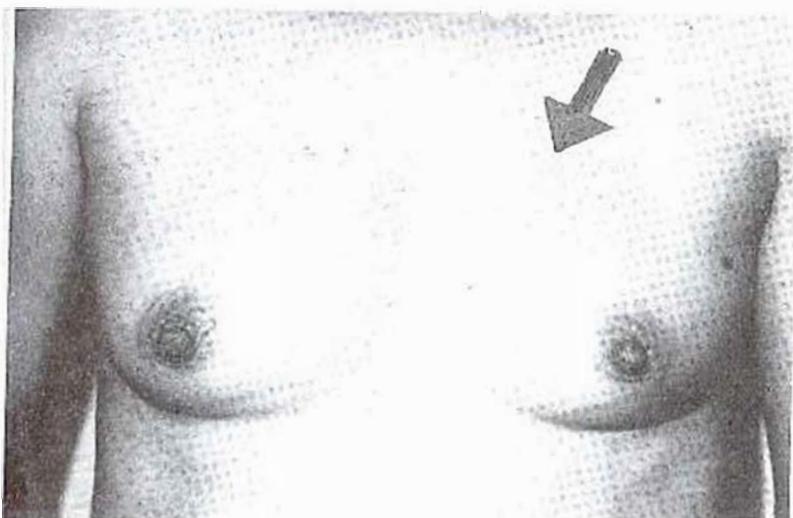


Figure 6. Accessory nipple or polythelia (*arrow*).



Figure 7. Embryonic milk lines.

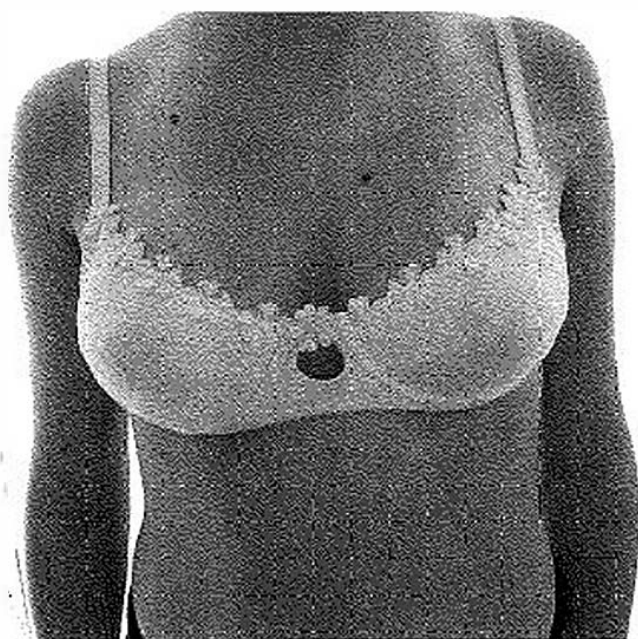


Figure 8. Hemangioma in the left breast in a 16 year old girl.

An inverted nipple is one that does not project beyond the breast surface and is noted at birth; it is typically bilateral and usually reverts to normal in a few weeks. If persistent into the adolescent years, cosmetic and lactation concerns often arise. The infraareolar breast tissue can be compressed and may lead to nipple protrusion. Infection can develop in an inverted nipple unless hygiene is excellent at all times and can lead to chronic areolar abscesses with swelling, erythema, pain, and discharge of the involved nipple (s). Management includes local heat application, antibiotics, and surgery to divide the breast ducts and raise the nipple; however, breast feeding potential is then typically compromised. Acute onset of nipple inversion in adolescence or adulthood suggests such problems as duct ectasia or malignancy that commonly presents as unilateral nipple inversion.

Other nipple anomalies include a bifid nipple (see figure 9) and a depressed nipple; the latter involves lactiferous ducts that directly open into a depressed areolar center and if severe, breast feeding is prevented. Management is with surgical correction as with the inverted nipple. The absence of a nipple, athelia, is a very rare condition and may also be seen as a unilateral, bilateral, and/or familial condition; it may occur with exposure to exogenous androgen taken during pregnancy.



Figure. 9. Bifid nipple. A rare breast anomaly that is a partial duplication of the nipple.

## **Polymastia/Amastia**

Polymastia or supernumerary breasts is noted less commonly than polythelia and like extra nipples (see figures 5,6), can be unilateral, bilateral, and/or familial. An extra breast (polymastia) or extra nipple (polythelia) occurs in approximately 1% of the population and may be an inherited condition (23). Supernumerary nipples are slightly more common in males than in females. The extrabreast tissue can be seen anywhere along the milk lines, but they are typically found below a normal breast, on the chest or upper abdomen. Various combinations of nipple, areola and glandular breast tissue can be seen, leading to confusion with other conditions, including hidradenitis suppurativa. The extra tissue may become readily apparent with puberty, pregnancy, and/or lactation. This accessory tissue is usually removed for cosmetic and/or diagnostic reasons, but other indications include an axillary location and the presence of lactation. There are rare case reports of a malignancy developing in supernumerary breast tissue (24). Another rare congenital anomaly of the breast is symmastia, with breast tissue webbing or confluence in the midline.

The absence of a breast (amastia) is rare and occurs because of complete mammary ridge involution, including the pectoral ridge on the affected side. Amastia, like athelia, can be associated with chest wall anomalies as pectus excavatum or the Poland syndrome. The Poland syndrome (see figures 10,11) describes a condition with various combinations of anomalies, such as amastia, pectoralis muscle aplasia, rib deformities, and upper limb defects (such as radial nerve aplasia and finger webbing) (1,2,4,9,14,25). Management includes surgical correction of the chest wall deformities. Amastia can be acquired because of damage from a breast bud biopsy, irradiation to the breast area, or other injury to breast tissue. An abnormal breast appearance can also be seen with pectus excavatum (see figure 12).



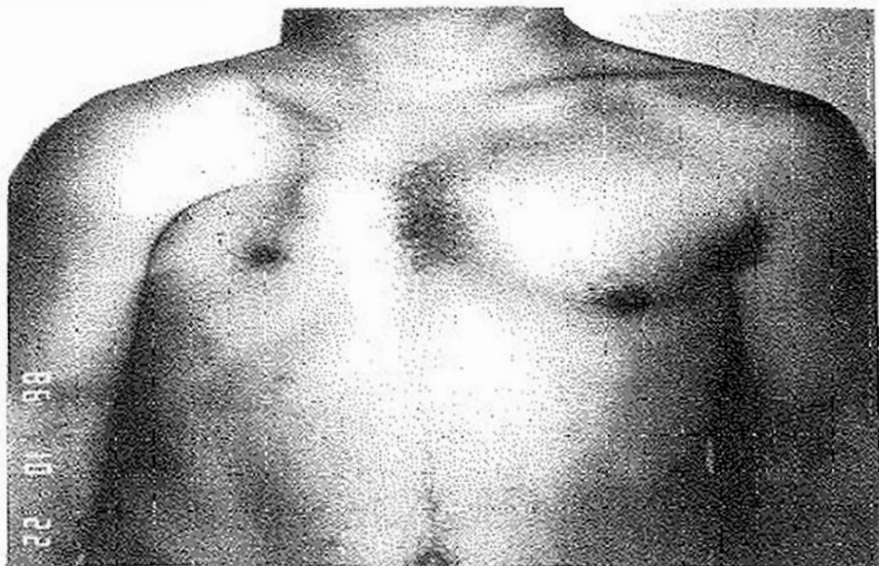


Figure 10. Poland Syndrome.



Figure 11. Poland Syndrome (same patient as figure 10, lateral view).

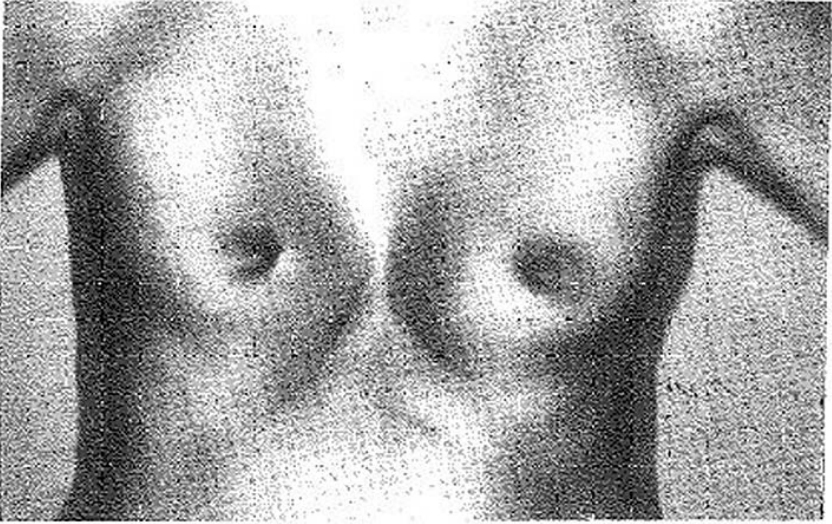


Figure 12. Pectus Excavatum. A classic chest wall deformity that can affect the breast appearance. Reconstructive surgery may improve the cosmetic appearance.

## TIMING OF BREAST DEVELOPMENT

Thelarche (onset of breast development) begins at an average age of 10 to 10 1/2 years of age with a normal variation of 6-8 years at the earliest to 13 years at the latest, and it is the first sign of puberty in females in most cases (26-28). The exact timing of how early breast development may arise before identifying it as premature remains debated by various experts. Some research suggests that thelarche may normally begin as early as age 6 years in African-American children and 7 years in Caucasian children; approximately 48% of African-American females have thelarche between 8 and 9 years of age versus 1.5% of Caucasian females (29). Thus, the definition of precocious puberty and delayed puberty may vary from expert to expert. Once breast development begins, it usually takes 2 to 3 years for full breast development, and about two to three years (1 1/4 - 4 years) for menarche (onset of menstrual periods) (26,28). Some females remain at SMR 3 until pregnancy and they can be reassured of the normalcy of these breasts in a world often obsessed with "full" breasts.

The average age of menarche dropped in the United States from the 1800s to the mid-1990s for reasons usually linked to improved nutrition and health as well as increased weight (26). There is no clear evidence that age of menarche continued to decline from the mid-1900s to the present and it appears to have stabilized at age 13 in Northern Europe. In less developed countries and those with warm climates, it appears to be still dropping (26). Earlier puberty may lead to earlier sexual activity with resultant complications of high risk behaviors, such as pregnancy, date violence, school failure, and others.

Premature thelarche (see figure 13) is defined by the isolated appearance of breasts in the female child under age 6 to 8 years of age without other evidence of puberty (such as pubarche or menarche) (4,30). It has a prevalence of 2% and typically, is noted between ages 1 and 3 years with normal laboratory studies (see table 3); sometimes, serum estradiol may be slightly increased. Table 4 lists potential causes of premature thelarche. A careful history is important to identify potential sources of exogenous estrogen exposure. Further evaluation reveals no estrogen effect on the vagina (i.e., vaginal cytology change), no further progression of breast tissue, and no other evidence of puberty (such as development of pubic hair, thickening of the vaginal mucosa, or accelerated bone growth). If no other signs of puberty are present, reassure the patient and family that this is a benign finding. Examine the child every 6-12 months; if other signs of puberty are evident, precocious puberty should be entertained as a diagnosis. In premature thelarche, the breast budding may persist until later puberty; if there is breast development beyond SMR 2, it typically regresses until later, usually normal puberty occurs.

**Table 3. Potential laboratory studies to evaluate premature thelarche**

Gonadotropins (LH, FSH)
Estradiol
Vaginal cytology
17-ketosteroids (urinary)
DHEA
Bone age
Ultrasound (uterus and ovaries)
Head CT/MRI (evaluate for pituitary/hypothalamic neoplasia)



Figure 13. Premature Thelarche in a 4 year old girl.

#### **Table 4. Causes of premature thelarche**

##### Genetics

Increased estrogen sensitivity

Increased estrogen (from the adrenal gland, dietary ingestion)

Oral contraceptive exposure

Transient secretion of estrogen from ovarian follicular cysts

Application of estrogen cream to the nipples

Transient activation (partial) of pubertal axis with increased FSH

Primary hypothyroidism (with elevated TSH and prolactin)

Sometimes premature thelarche represents an incomplete and benign form of precocious puberty, requiring periodic observation and reassurance. Early onset of puberty is more common in girls than in boys and is predominantly mediated by premature activation of the hypothalamic-pituitary-gonadal axis (30). Central (true) precocious

puberty may be caused by hypothalamic hamartomas, trauma, hydrocephalus, and central nervous system lesions; however, it is most commonly idiopathic. Treatment depends on the underlying etiology. Gonadotropin-releasing hormone (GnRH) analogues are used to postpone puberty until an appropriate age and it could be helpful to optimize adult height potential (31).

Peripheral precocious puberty (pseudo-precocious puberty) is due to sex steroid secretion independent of gonadotropin release, and it is much rarer than true precocious puberty; its causes include an estrogen-secreting tumor and the McCune-Albright syndrome. When suspecting precocious puberty, tests to obtain include luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), thyroxine (T4), testosterone, and estradiol. If premature breast development arises along with other secondary sex characteristics, the diagnosis becomes precocious puberty and a careful evaluation is necessary for underlying organic causes (see table 5). Management is dependent on the underlying etiology. When hirsutism or virilization occurs with precocious puberty, adrenal tumors or late-onset adrenal hyperplasia must be excluded.

**Table 5. Causes of precocious puberty (partial list)**

Idiopathic (80-90% in females and 40% in males)
Ovarian neoplasm in females or testicular tumor in males (10% vs. 15% respectively)
McCune-Albright syndrome (5% of females and 1% of males)
CNS pathology (as neoplasm) (5-10% in females and 25%+ in males)
Adrenal neoplasm/hyperplasia (1% in females and 25% in males)
Hypothyroidism (rare)

## BREAST ASYMMETRY

It is common for young adolescent females to have breast asymmetry; in some youth, one breast bud appears before the other starts while in some youth, asymmetry emerges after bilateral thelarche develops (4,9). Familial or genetic factors influence the timing of

puberty, the appearance of thelarche, and the rate of breast growth on both sides. Adequate symmetry eventually develops in most females by late adolescence. though approximately 25% of adult females have visible asymmetry (see figure 14). Padding the smaller side may help while waiting to see if acceptable catch-up growth will take place as adolescence continues. Youth should be advised to avoid worthless "bust developers or pumps" that are sometimes advertised, though exercise can develop improved pectoralis muscle tone, partially improving the breast appearance. Application of estrogen cream is not recommended by most clinicians since the less developed breast may lack estrogen receptors. Pseudoasymmetry may be present because scoliosis or a rib cage defect gives the illusion of unequal breast size.

Also, a breast may not grow properly because of prepubertal injury, trauma, or surgery that includes improper biopsy of a lesion that is actually a breast bud (1). In very young and preadolescent children, a biopsy should be considered with extreme caution because the developing breast bud may be irreparably harmed, even with a needle aspirate. Thoracostomy tube insertion, anterolateral thoracostomy, infection, and burns may also lead to breast damage. Burns usually lead to scarring with normal underlying breast tissue; the skin contractures should be released by early adolescence to allow normal breast development.

Transient or permanent breast asymmetry can lead to considerable embarrassment and psychological distress. There may be a positive family history for delayed puberty. The small breast may represent partial end-organ failure or the larger breast may be due to a breast mass (see figure 15), as discussed later in this article. Surgery is the typical method of management for significant breast asymmetry when the patient is mature enough to understand the surgical options as well as risks, and provide legal consent. Surgery should be decided on by the youth in late adolescence or early adulthood so the patient is cognitively mature enough to make such a decision and also to allow for full development of both breasts that includes full catch-up growth of the smaller breast.



Figure 14. Breast Asymmetry. Of particular interest is the difference in size of the nipple - areolar complex and the overt difference in their location.

Reconstructive surgery includes a combination of augmenting the smaller breast or reducing the larger breast.

One breast may be enlarged and/or the other reduced, depending on the precise situation. Augmentation mammoplasty has been a controversial procedure and the youth should clearly understand the potential benefits and risks associated with the procedure being offered. Surgical complications may include severe scarring, confusion with cancer later in life, and lactation dysfunction; also, innervation of the nipple is from the fourth intercostal nerve and surgical damage to this nerve may lead to loss of erotic sensation [32]. Sometimes it is not the breast volume that is of concern, but the breast shape that requires a breast lift or mastopexy.

## UNDERDEVELOPED BREASTS

Another common concern of some adolescent females is that of small breasts (micromastia; hypoplasia) (1,2,9). It may be found in someone simply in early puberty or in someone in later puberty with an otherwise

normal examination and normal estrogenization (i.e., normal pubic hair, vagina, uterus, and female appearance), along with a normal menstrual history. Reassurance of normalcy is important, though breast enlargement surgery (augmentation mammoplasty) may be chosen at some point by this patient (32).

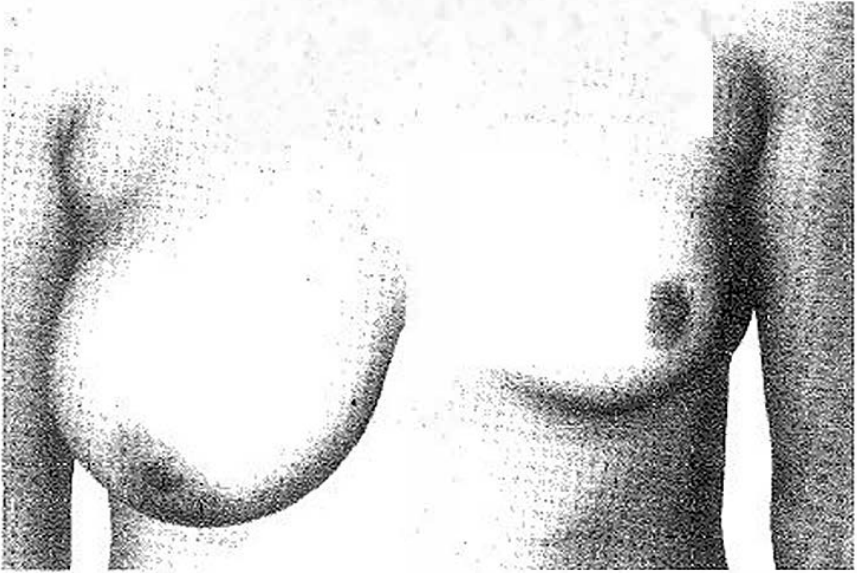


Figure 15. Breast asymmetry due to a right breast lipoma.

However, an evaluation may reveal variable degrees of bilateral hypoplasia or hypomastia plus ovarian dysfunction (see table 6) with failure of secondary sex characteristics and typically primary amenorrhea. The nipples are then abnormal as well—less pigmented, less protuberant, and smaller. A complete genetic and endocrine work-up is then recommended. Appropriate management of the underlying disorder is important, as hormonal management of Turner syndrome, for example.

**Table 6 Causes of bilateral breast hypoplasia and ovarian dysfunction/hypofunction**

Gonadal dysgenesis (Turner syndrome)

Adrenal hyperplasia (as congenital adrenal hyperplasia)



Pituitary hypogonadism
Preadolescent hypothyroidism
Androgen-producing tumor
Radiation effects
Bilateral ovariectomy
Malnutrition
Deficiency of body weight (BMI<18.5)
Some chronic illnesses
Delay of sexual development
Amenorrhea

## TUBEROUS BREASTS

An unusual breast deformity has been described by Rees and Aston as tuberous breasts (tuberous breast anomaly) because the breasts have the appearance of a tuberous root plant (see figures 16,17) (4,33). There is limitation in the breast base horizontally and vertically in which the breast projects forward without normal fullness, but with an enlarged, overdeveloped nipple areola complex. Two types are described, Type 1 and 2. Type 1 is the usually tuberous breast presentation with a small concentric breast base and a large nipple areola complex that represents herniation of breast tissue into the areola. The less common type, Type 2, presents with a breast that is more deficient in its vertical than horizontal dimension and has a small breast base. Management of type 1 is with augmentation of these hypoplastic breasts and reduction of the herniated breast tissue from the nipple areolar complex. Type 2 is treated with augmentation of these hypoplastic breasts. Mild cases may not require plastic surgery.

## BREAST ATROPHY

Breast atrophy may develop after thelarche from various causes (see table 7) leading to breasts that become wrinkled, flattened, ptotic, and senile in appearance (1,2,4). Both the adipose and glandular tissues can

be severely reduced. Restoration of the previous normal breast tissue is unlikely; however, some improvement may occur primarily with correction of the underlying problems and the use of oral contraceptives - if appropriate for those with **an** eating disorder (see figure 18) or other chronic illness. For example, scleroderma can cause variable amount of breast tissue atrophy.

### Table 7. Causes of breast atrophy

Weight loss from severe dieting (especially a protein-poor diet)
Anorexia nervosa
Premature ovarian failure
Scleroderma
Other chronic illnesses causing significant weight loss

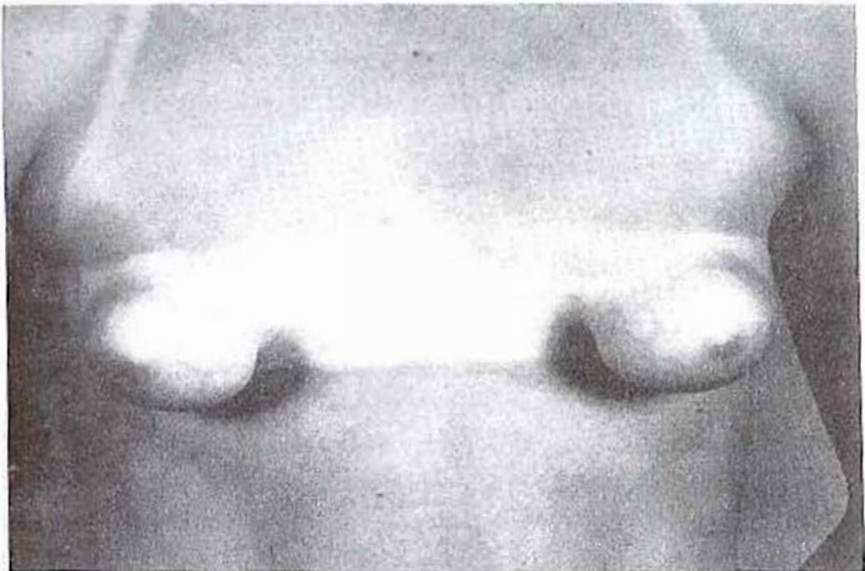


Figure 16. Tuberosus Breast Anomaly (Type I).

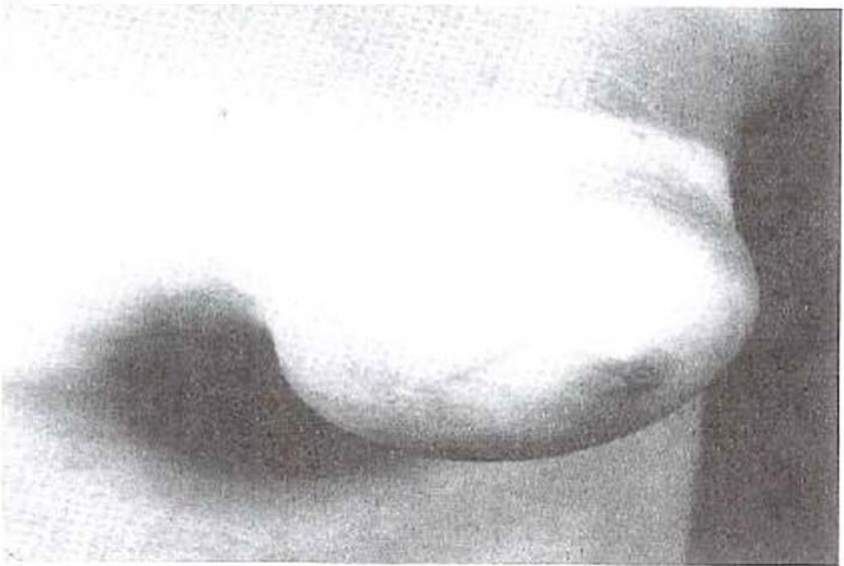


Figure 17. Tuberous Breast Anomaly (Type I). A closer view of Figure 16

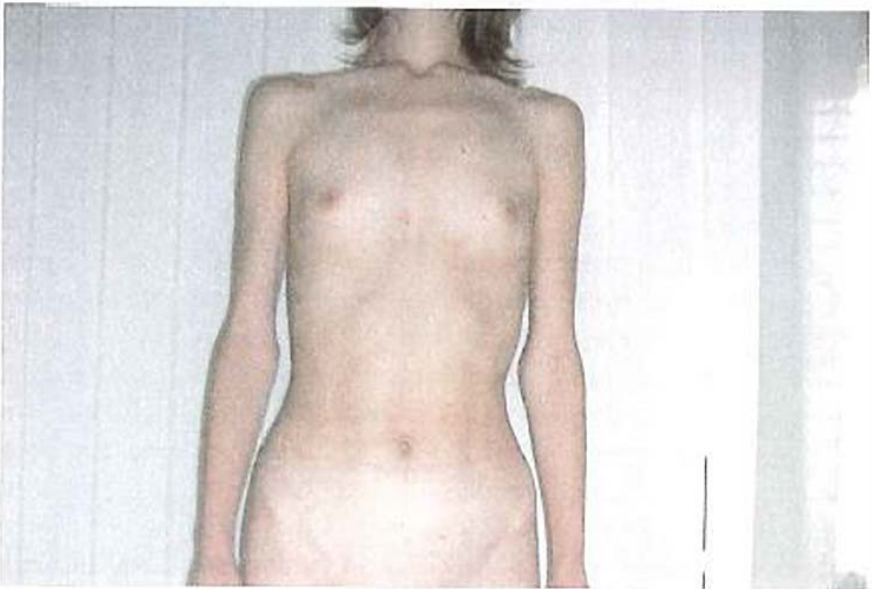


Figure 18. Hypoplasia of breasts in a patient with Anorexia Nervosa, 17 years old.

## MAMMARY HYPERPLASIA

The condition in which breasts enlarge in the newborn period is called neonatal breast hypertrophy and development of large breasts during puberty has many terms, including mammary hyperplasia or idiopathic breast hypertrophy. Neonatal breast hypertrophy can be noted in as many as 70% of newborns (females and males) and is usually attributed to maternal estrogen effects and/or an abnormal ratio of estrogen to androgen. Enlarged breasts are usually less marked in premature infants, presumably since immaturity does not allow as much breast reaction as noted in more mature newborns. The normal post-delivery withdrawal of maternal estrogen can lead to increased prolactin levels and the enlarged breasts in the newborn may produce a clear or cloudy (milk-like) nipple discharge ("witch's milk"). Frequent breast stimulation may lead to hyperplasia, nipple discharge, and mastitis. The hyperplasia usually resolves in a few days to few weeks, though there are case reports of breast hypertrophy lasting up to 10 months in males and 2 years in females. Breast carcinoma in infants with breast hypertrophy is extremely rare.

### Juvenile (virginal) breast hypertrophy

In this situation, there is explosive breast growth often shortly after thelarche that is unilateral or bilateral and often familial (see figures 19,20) (4,34). Extreme growth can rarely be seen and is called macromastia or gigantomastia, as noted by one case report in a 4'10", 106 pound, 12-year-old whose left breast weighed 3,800 grams and right breast weighed 4,200 grams (1). The etiology is usually attributed to heightened response or sensitivity of breast tissue to pubertal hormones and endogenous hormone production from breast cells. Exposure to estrogen has been noted in some cases, as breast hypertrophy developing while on oral contraceptives. It also occurs during pregnancy. Juvenile hypertrophy appears to be more common in African-American females than Caucasian females. Potential sequelae are many, as listed in table 8 (1,2,9). The differential diagnosis of unilateral hypertrophy includes a breast tumor, typically a giant fibroadenoma.

Table 8. Potential complications of breast hypertrophy

Extreme embarrassment (for patient and family)
Unwanted attention from males
Secondary psychological difficulties
Severe neck or back pain
Poor (kyphotic) posture
Headaches (due to neck strain)
Dermatitis and ulceration
Breast tissue necrosis
Stretching and flattening of the areolae
Difficulty with various physical activities, including sports
Problems with finding proper fitting clothes
Brachial plexus-induced paresthesias
Massive enlargement: thoracic compression
-Respiratory distress
-Spinal curvature



Figure 19. Bilateral Mammary Hyperplasia in a 14 year old girl. Also has polythelia on the right breast

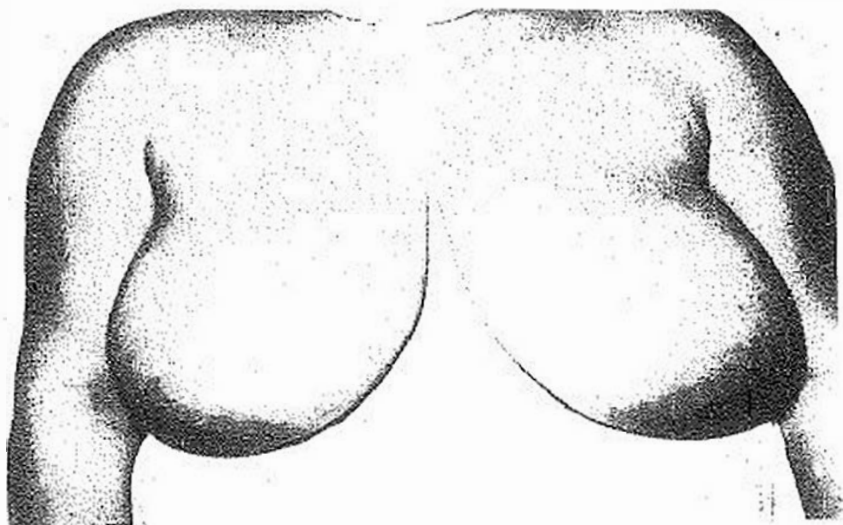


Figure 20. Idiopathic breast hypertrophy in an adolescent.

Management must be individualized and ranges from reassurance that the breast tissue is normal (with firm bra support), to surgery in order to reduce the breast size (9,35). There may be some regression of the hyperplasia later in adolescence, though this is typically mild if at all. Research has noted that medication (such as danazol, medroxyprogesterone, or dydrogesterone) used in adult females is not effective in management of mammary hyperplasia in adolescents and has a number of adverse effects, depending on which medication is used.

It is recommended that surgery, if chosen by the patient, be done at a time when final breast enlargement has occurred or the breasts are mature and the patient is mature enough to decide if as well as when this surgery should be accomplished (32). Surgery done earlier because of severe problems (see table 8) may be complicated by later recurrent hypertrophy as the breasts continue to grow. The surgery is reduction mammoplasty for unilateral or bilateral hyperplasia and the precise technique depends on the training of the surgeon. Post-operative complications include breast hematoma, infection, wound drainage, and fat necrosis. Other surgical sequelae include breast scarring (can be severe), loss of nipple sensation (5-25%), and lactation dysfunction. A link between cosmetic breast augmentation and suicide in adult women has been identified (36).

## FIBROADENOMA

Fibroadenoma is the most common breast tumor in adolescent females, noted in 70% to 95% of breast biopsies in this age group; it is the most common cause of a solid breast mass in females from puberty to age 30 (1,2,4,9,14,22,37-40). In Stone's classic **series** of 165 youth between ages 11 and 20 years, 72% had a fibroadenoma in contrast to 12% with hyperplasia, 7% with an abscess, 6% with breast cystic disease, and 3% with intraductal papilloma (41). In Hein's review of 95 adolescents, 75% with biopsies had a fibroadenoma, in contrast to 12% with an abscess, 10% with cystic disease, 2% with a lipoma, and 2% with cystosarcoma phyllodes (42). Table 9 provides a list of breast mass pathology.

A fibroadenoma typically presents as a rubbery, non-tender, encapsulated mass slowly increasing in size over weeks to months (see figure 21). Sometimes it is seen as an irregular or oval lump with a consistency that can vary from elastic to hard versus the typical rubbery type; nipple discharge is not noted. The lesion can be seen anywhere in breast tissue, though the upper, outer quadrants are the most common. It usually is 3 cm to 4 cm when found, but can continue to enlarge to 10 or 15 cm if not removed in time. Large lesions can induce a malignancy-like state with *peau d'orange* skin having erythema and enlarged veins overlying the tumor. Bilateral or multiple tumors, often called fibroadenomatis, are noted in 10% to 25% of cases.

**Table 9. Causes of breast masses\***

Fibroadenoma	Miscellaneous
Juvenile (giant) fibroadenoma	Nipple adenoma
Other fibroadenoma variants	Papillomatosis
Virginal hyperplasia	Ductal adenocarcinoma
Cystosarcoma phyllodes	Mammary duct ectasia
Breast abscess	Intraductal granuloma
Breast cyst (including fibrocystic Breast disease and other Breast mastopathies)	Sclerosing adenosis
Breast carcinoma	Keratoma of the nipple
Intraductal papilloma	Interstitial fibrosis
Fat necrosis	Granular cell myoblastoma

Lipoma	Angiosarcoma of the breast
Lymphangioma	Metastatic disease (e.g., leukemia, malignant lymphoma, ovarian malignancy, others)
Hemangioma	Neurofibromatosis
	Dermatofibromatosis
	Tuberous mastitis
	Papilloma sarcoidosis
	Hematoma
	Others

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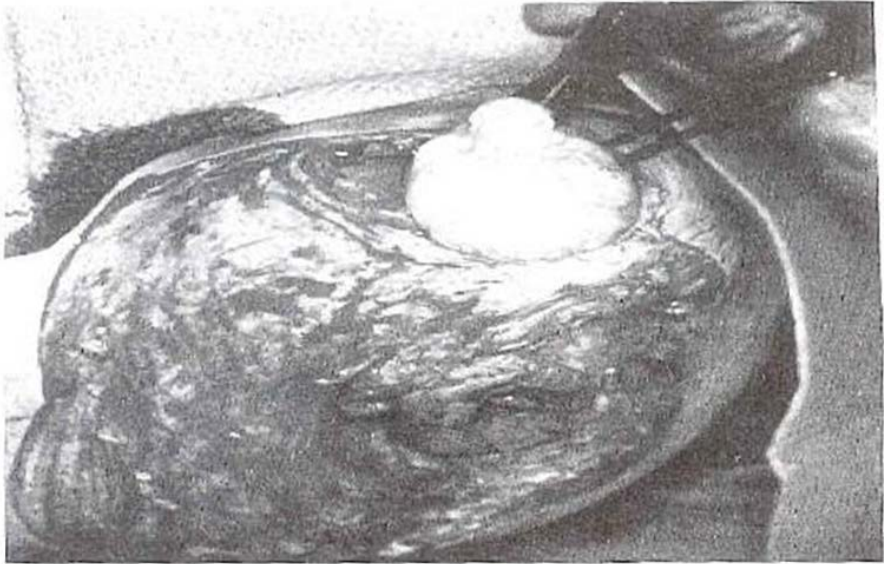
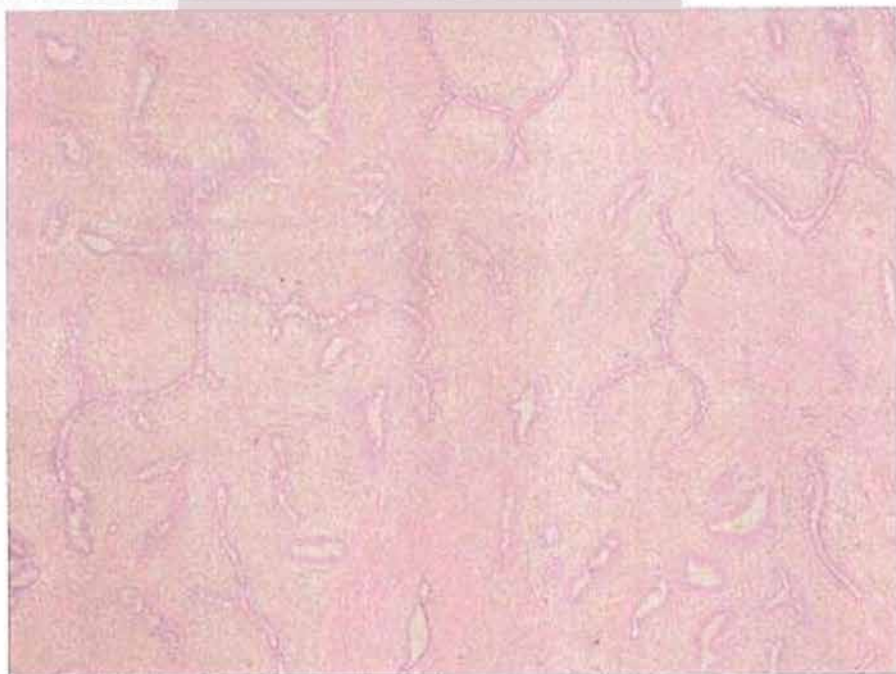


Figure 21. Fibroadenoma. Lesions can be diagnosed by needle aspiration and effective treatment is total excision. For needle biopsy, use a 1<sup>1/2</sup>-inch 22-gauge needle attached to a 12-ml syringe and use aseptic technique. Fix the mass between your fingers and place the needle into it. Entering a fibroadenoma, as this one, is like placing a needle into a rubber eraser, while entering breast cancer, the aspirator notes firm resistance and a characteristic feeling while entering microcalcifications of the tumor. A "popping" sensation is felt while the needle enters acyst as the mass disappears.

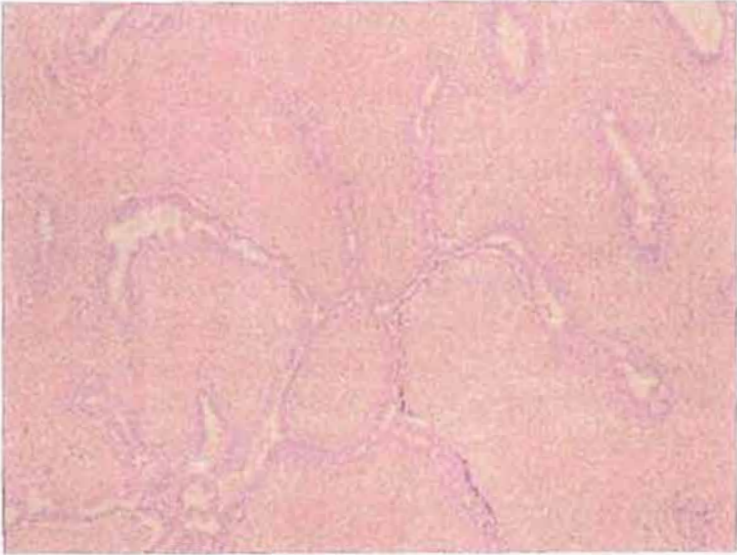


Fibroadenomas are estrogen-sensitive tumors that can develop from breast lobules and stroma at any time during adolescence, from 2 years before menarche to the more typical late adolescence limiting of 17 to 20 years of age; estrogen receptors are found in this tumor. Development of these tumors tends to decrease by the mid-to late 20s (22). It is found in all ethnic groups, though it is more common in African-American females. Enlargement may occur late in a menstrual cycle and especially during pregnancy; spontaneous regression may occur, but is not the norm. The typical biopsy reveals a pattern similar to virginal hyperplasia and male gynecomastia with ducts that are elongated in a stroma that is fibrous (see figures 22-24); a number of histologic variants are noted and classified according to tumor size and stroma cellularity (1,2,4). Figure 25 reveals the ultrasound appearance of fibroadenomas.



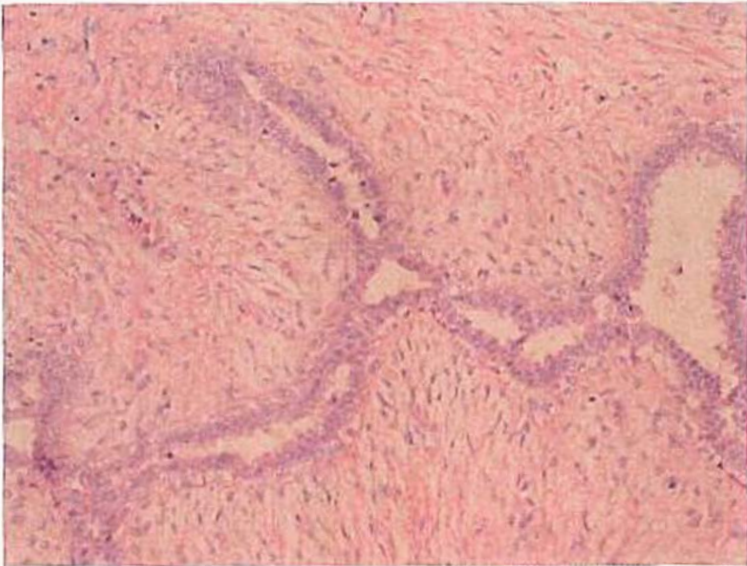
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Figure 22. Fibroadenoma Histology.



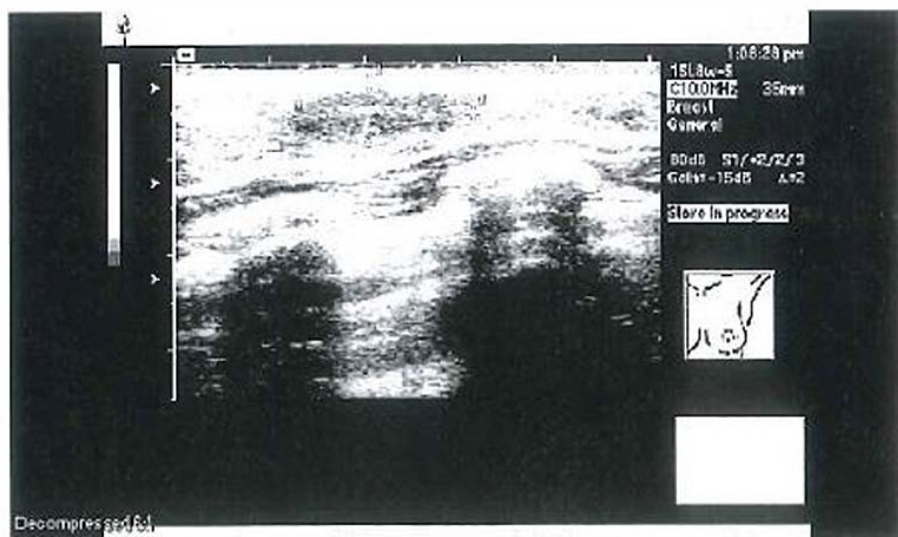
Used with permission from Jeffrey Pearson, MD, Medical Director, Pathology Department, Bronson Hospital, Kalamazoo, Michigan Figure 24. Fibroadenoma Histology.

Figure 23. Fibroadenoma Histology.



Used with permission from Jeffrey Pearson, MD. Medical Director. Pathology Department, Bronson Hospital, Kalamazoo, Michigan

Figure 24. Fibroadenoma Histology.



Used with permission from Kathleen Gadwood, MD, Ultrasound Division, Radiology Department, Bronson Hospital, Kalamazoo, Michigan.

Figure 25. Ultrasound: Fibroadenoma. 13 year old, left breast masses. The patient presents with two palpable masses in the medial and inferomedial left breast. On palpation, these masses are freely movable with a rubbery consistency. They are nontender. Targeted ultrasound shows the largest mass located medially is oval, well-circumscribed with a thin capsule, long axis parallel to the skin, measuring 3.3 x 3.3 x 0.8 cm. This is located in a very thin portion of breast tissue. The other nodule is located just medial and inferiorly, and measures 1.9 x 1.1 x 0.8 cm. This has a similar echo appearance. Impression: Benign findings. The sonographic appearance would be consistent with two fibroadenomas.

Though the differential diagnosis of a breast mass or lesion in an adolescent is quite extensive (see table 9), the diagnosis of fibroadenoma is usually considered in typical presentations. Malignancy is often the concern of the patient and her parents; fortunately, this is quite rare in the adolescent population and there is no proven link between the presence of a fibroadenoma and later breast cancer development (4, 44). The timing of the tumor removal varies according to the tumor's presentation, size (some consider surgery only if the tumor size is > 2 cm), concern of the patient and/or parents, how quickly the lesion grows, and other factors. It is not possible to predict the growth of a fibroadenoma; some spontaneously involute over several months, some grow slowly, and some remain dormant for many years.

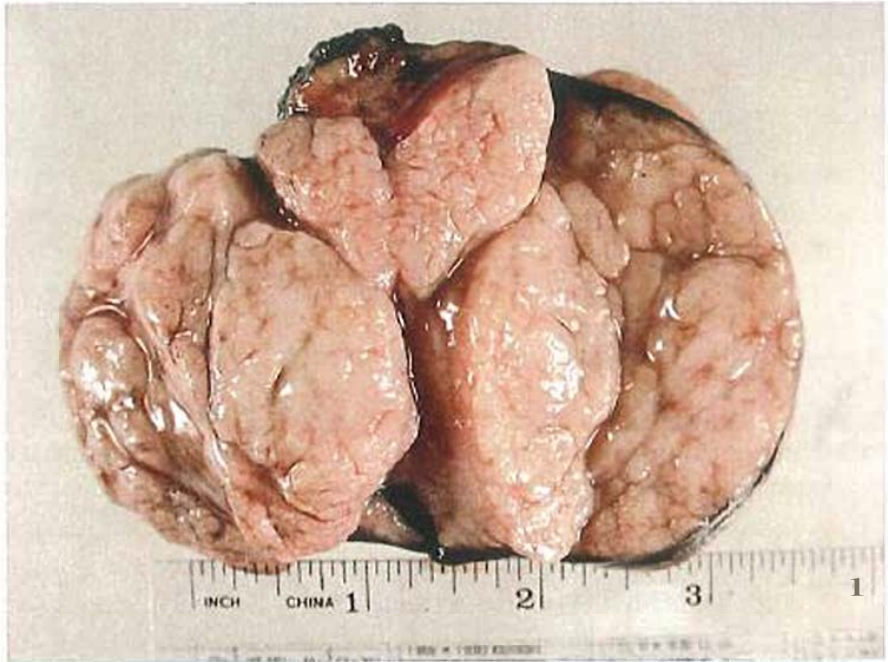
Discrete breast masses should almost always be removed in boys and postpubertal girls. Excisional biopsies are usually performed using a circumareolar incision; if the mass is distant from the areola, an incision directly overlying the mass may be performed. A small and slow-growing lesion in an adolescent female that is rubbery and non-tender can be observed over 2 to 4 months. Novel non-steroidal selective antiestrogen drugs have also been administered in those with fibroadenoma, with a reported result of 40% disappearance and 20% partial regression (43,45). Minimally invasive procedures for management of fibroadenoma include percutaneous radiofrequency-assisted excision and cryotherapy (46,47).

One should certainly not wait until the lesion is large, as this may require more extensive surgery to remove the tumor, increasing the risk of breast deformity, and making skin closure more difficult. Expert surgical technique is important for the youth with a young, growing breast; for example, protection of the developing nipple, areola, and other breast tissue is as important as excision of the lesion. Waiting until the tumor is large may also require additional surgery to reduce the skin envelope and elevate the nipple for a good cosmetic result. If a unilateral lesion presents, excision, biopsy can rule out cystic breast disease, virginal hypertrophy, cystosarcoma, phyllodes and other conditions. A lesion that enlarges rapidly must be distinguished from virginal hyperplasia, giant fibroadenoma, and cystosarcoma phyllodes. If a patient presents with fibroadenomatosis, the largest lesion should be removed to establish the diagnosis and prevent breast deformity. If there is evidence of malignancy, immediate investigation with complete lesion removal is indicated.

## GIANT (JUVENILE) FIBROADENOMA

The giant or juvenile fibroadenoma is larger than 5 cm in diameter, sometimes doubling in size within 3 to 6 months, up to 15 or 20 cm; it may compress or replace normal breast tissue (see figures 26 and 27) (1,2,4,9). It is less common than the normal fibroadenoma, but, like the typical fibroadenoma, the giant variant is more common in African-American youth and peaks in incidence in late adolescence; it tends to be

more common than the smaller version in the young adolescent and its consistency tends to be softer than the rubbery consistency of the smaller fibroadenoma. Adjacent breast tissue can be compressed and distorted by the size and rapidity of growth of a giant fibroadenoma, leading to overlying skin ulceration.



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Figure 26. Giant (Juvenile) Fibroadenoma.

Complete removal of a large lesion may be difficult because of its size and the difficulty separating out normal tissue margin from tumor margin. A number of histologic variants are described and are sometimes confused with cystosarcoma phyllodes. The typical biopsy of a giant fibroadenoma reports increased stromal cellularity and fibrosis. The lesion can be single, recurrent, or even found posterior to breast tissue; in the later case, the larger breast has increased warmth because of increased blood in the tumor and distended veins overlying the involved skin. A tumor with severe atypical epithelial hyperplasia may cause confusion with malignancy.



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Figure 27. Giant (Juvenile) Fibroadenoma.

## CYSTOSARCOMA PHYLLODES

Though breast malignancy is rare in the adolescent, the main type noted is cystosarcoma phyllodes (phyllodes; Greek: phyllon leaf) (1,2,4,9,14,48,49). Its original description by Muller in 1838 included the idea that this tumor arises from a fibroadenoma, leading to many decades of linking these two lesions (1,2). At present, there is no evidence cystosarcoma phyllodes arises from a fibroadenoma. Proposed etiologic factors for cystosarcoma phyllodes include pubertal hormonal effects (including excess estrogen), pregnancy, lactation, and trauma. It can be associated with a variety of tumors, such as intraductal breast carcinoma, Brenner tumor of the ovary, desmoid tumor, and scirrhous breast carcinoma.

Cystosarcoma phyllodes can be found in all decades of life, peaking in the fourth decade. In adults it represents 0.3 to 0.9 percent of all breast tumors and though most are benign, metastatic disease is found in 3% to 12% (or more). Approximately 5% to 8% of cases occur in those under age 20, mainly between ages 16 and 19 years of age and most are benign (1,2,48). However, rare cases of malignant disease with death are reported in the literature in adolescent females as well as cases of cystosarcoma phyllodes in prepubertal children and even adolescent males with gynecomastia.

Cystosarcoma phyllodes usually presents as a painless, slow growing breast tumor that is typically 8 cm to 10 cm when found. However, its growth may be explosive and symptoms are dependent on the size and location of the tumor. There may be a large tumor (up to 20 cm) with overlying shiny skin that is stretched and contains distended veins, erythema, and skin ulcers. There can also be local tissue compression (with parenchyma necrosis), nipple retraction, bloody nipple discharge, and in 20% of cases-axillary lymphadenopathy (from infection and tumor necrosis, not usually overt metastasis). In the unusual adolescent case with tumor metastasis, spread is hematogenous and the lung is the most common area involved, though any organ invasion is possible. The tumor size does not reflect malignancy and three basic histologic patterns are described: benign, intermediate (borderline), and malignant.

A benign type has less encapsulation and more cellular stroma than a fibroadenoma; a malignant lesion has cellular atypia, anaplasia, and mitotic activity.

An ultrasound may give a fibroadenoma-like appearance or give a cystosarcoma phyllodes-like appearance of fluid-filled, elongated spaces or cleft within a solid tumor. As previously noted, mammograms are usually not helpful in adolescent females because of their dense breast tissue. Management depends on total tumor removal, results of the histologic study, and evidence of metastasis. The tumor must be fully excised, leaving margins free of tumor and tumor appendages. The management of intermediate or overt malignant cases remains controversial and the prognosis is often poor. Various treatments are used including radical surgery, chemotherapy, radiation therapy, and hormonal treatment (1,2,4,9,14,48,49).

## INTRADUCTAL BREAST PAPILOMA

This is a rare tumor in the adolescent population, usually presenting as a small lesion under the areola that produces sanguineous or sero-sanguineous discharge from the nipple (1,2,4). It may be quite small and only found with careful palpation in the subareolar area. Sometimes a tumor is not felt, but palpation compresses a duct that is distended with the tumor, leading to the typical nipple discharge. Intraductal breast papilloma is bilateral in 25%, and cytology of the nipple discharge notes clusters of ductal cells. Table 10 lists the differential diagnosis of intraductal breast papilloma. Helpful diagnostic aids include ultrasound and fine needle aspiration. Intraductal breast papilloma is a benign lesion (though some experts classify it as a pre-malignant condition) and local excision cures the condition. Infiltrating ductal adenocarcinoma is a very rare malignant disorder in adolescents that requires radical mastectomy and radiation therapy.

Table 10. Differential diagnosis of intraductal breast papilloma

Fibroadenoma
Nipple adenoma
Cystosarcoma phyllodes
Papillary carcinoma
Mammary duct ectasia
Ductal hyperplasia
Juvenile papillomatosis with cystic lesions
Papillary duct hyperplasia (non-cystic lesions)
-Solitary papilloma
-Papillomatosis (epitheliosis)
-Sclerosing papillomatosis
-Multiple papillomas
Infiltrating ductal adenocarcinoma

Mammary duct ectasia (periductal mastitis) presents with a nipple discharge (dark-brown) because of dilatation or ectasia of ducts behind the nipple; there can be a painful subareolar nodule with nipple retraction, sinus tracts or fistulae, and axillary lymphadenopathy. It is the



most common cause of nipple inversion and there can be infection with *Bacteroides* sp. Management includes antibiotics, sinus tract/fistulae excision and sometimes, excision of part or all of the involved nipple.

## BREAST CANCER

Breast cancer (i.e., adenocarcinoma) is a rare disorder in adolescent females; however, it is on the mind of the patient (and parents) when she presents with a breast mass (1,2,4,50-53). Breast cancer is found in less than 2% of females under age 25, less than 1% in those under age 20 years of age, and rarely in those under 15 years of age. However, it is reported in youth and very rarely in prepubertal children, and thus, must be part of the differential diagnosis of a breast mass in children and adolescents. In very rare cases it has been reported in males (52,54,55).

Risk factors are noted in table 11 and improved prognostic factors in table 12 (1,2,9,14,56). A positive family history for breast cancer is a very high risk factor (30-50%), especially with certain syndromes, as noted in table 9. Those with BRCA1 or BRCA2 gene mutations are noted in 8 of 10 familial breast cancers and 5% of all breast cancers (1,2,9,56). The decision to test for these gene mutations in female adolescents with a positive family history for breast cancer is based on various factors including the age of the adolescent, legal consent issues, and others. Though controversial, there is no clear link between the use of oral contraceptives and later development of breast adenocarcinoma (57). However, breast cancer is found in association with other cancers, as that of the ovary, uterus, and colon. Two-thirds of breast cancer found in adolescents are malignancies arising in non-breast tissue, such as secondary sarcomas (fibrosarcoma or liposarcoma) and metastatic disease due to lymphoma, leukemia, Hodgkin's disease, or multiple myeloma (57,58).

**Table 11. Risk factors for breast cancer\***

Positive family history of breast cancer	Nulliparous status; not breast-feeding
-BRCA1 (chromosome 17q)	Benign breast disease (see text)
-BRCA2 (chromosome 13q)	Hormone replacement therapy (HRT)
	(especially HRD ?Oral contraceptive pill?)
Miscellaneous syndromes	Delay of first pregnancy (after age 30)
SBLA Syndrome (Li-Fraumeni)	Radiation exposure
(especially the chest)	
Cowden's Syndrome	Increased dietary fat
(proposed)	
Muir Syndrome	Obesity (proposed)
Klinefelter syndrome (males)	
Others	Moderate or more alcohol consumption
Early puberty and early menarche (as Hodgkin's disease)	History of childhood cancer

- Used with permission from: Greydanus DE, Farrel(s) D, Farrell E. Disorders of the breasts in children and adolescents. *Pediatr Clin North Am* 1989;36(3):625.

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**Table 12. Good prognostic factors for breast cancer\***

Stages I and II
(Stage I: tumor is under 2 cm in diameter and there are no lymph nodes or distant metastasis; Stage II: tumor is under 5 cm in diameter. the palpable lymph nodes are not fixed, and there is no distant metastasis).
Positive estrogen receptor status
Secretory histology type
Circumscribed tumor edge (versus infiltrative)
Lateral location (versus medial)
Tumor under 2 cm in diameter
Absence of lymphadenopathy, nipple involvement, and cutaneous inflammatory changes

- Used with permission from: Greydanus DE, Parks D, Farrell E. Disorders of the breasts in children and adolescents. *Pediatr Clin North Am* 1989;36(3):625.

Though breast cancer is rare in the adolescent, it does exist and this risk increases considerably as she enters her adult years (see figure 28). Issues of self-breast examinations in adolescent females have been considered earlier. Screening mammograms are not helpful in most youth because of their normally dense breast tissue, as previously noted (see figure 29). The role of prophylactic mastectomy for those considered at high breast cancer risk should be made in consultation with a gynecologist recognized in this area; it is a controversial step, but one that patients can consider. Adult females with benign breast disease that increases their risk for breast cancer may be offered prophylactic tamoxifen (22).

Adenocarcinoma presents in the adolescent female as a non-tender, indurated, hard, single mass; it has indistinct margins, is typically fixed in the breast tissue or chest wall, and ranges from 1 cm to 9 cm at discovery. There may be skin edema, (peau d'orange), nipple discharge, retraction of the skin or nipple, and/or lymphadenopathy (axillary or supraclavicular). Metastatic disease may induce generalized skin rash, dyspnea (with pleural effusion), upper or lower limb swelling, back pain, hepatomegaly, and/or other features indicating spread of the primary cancer. A variety of diagnostic procedures are used, including mammography, ultrasonography, thermography, and DTPA breast scintiscanning. A CT or MRI can be helpful to differentiate a breast mass from a rib lesion or other chest wall pathology, or identify normal tissue (versus a mass, including a hemangioma or lymphangioma). The most reliable way to differentiate breast cancer from more common benign breast masses is the triple assessment, including palpation, radiology (mammography, ultrasound, and MRI scan), and fine-needle aspiration cytology (59).

An open or closed biopsy obtains tissue for a definitive pathological diagnosis, noting whether the cancer has developed from the secretory part of the breast (lobules) or the duct connecting the lobules to the nipple; it can be invasive or in situ. As noted, the cancer is an adenocarcinoma, often secretory, though other types are also less frequently identified (i.e., papillary, medullary, infiltrative, serous, glandular, inflammatory, colloidal, and mixed). Metastatic disease may develop, involving bone (often the back), lungs, liver, and other sites; it can be monitored with a variety of biochemical markers, such as

carcinoembryonic antigen, alkaline phosphatase, and hydroxyproline. Breast sarcomas and secondary malignancies (from leukemia or malignant lymphomas) are rarely noted as well. There may be a second cancer in an adolescent whose first cancer (i.e., leukemia, non-Hodgkin's lymphoma) occurred when the patient was a child, a metastatic neuroblastoma, a cancer due to previous chest wall radiation, and others. Management should be under the care of a specialist trained in current techniques of treatment, as well as understanding of the adolescent patient and her family.



Figure 28. Breast Cancer.

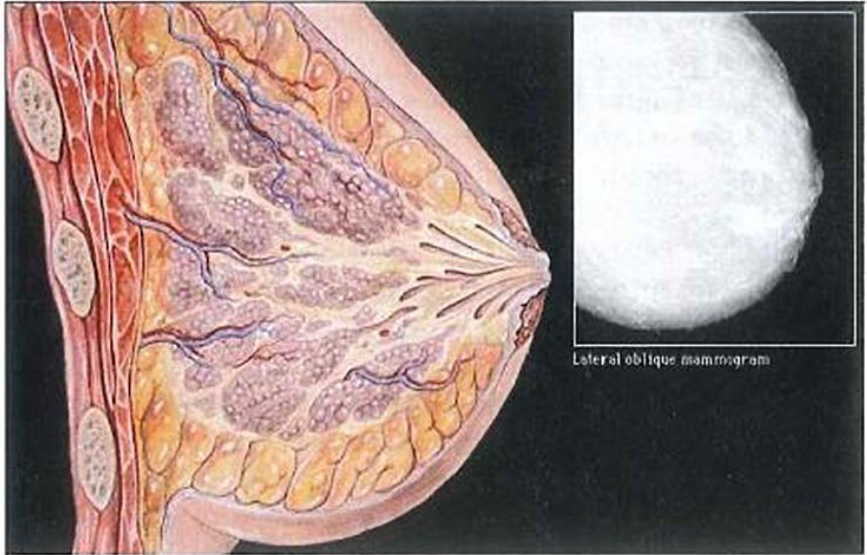


Figure 29. Breast Anatomy and Mammography.

## BREAST INFECTIONS

### Pre-pubertal infections

Neonatal breast hyperplasia can be complicated by infection from too much clinician examination or over-manipulation, as noted earlier. Mastitis can develop in neonates (mastitis neonatorum) involving the entire breast bud and can be complicated by septicemia (1,4,9). Mastitis can also develop in the prepubertal child, though septicemia does not usually occur. Antibiotic therapy is important to help resolve this infection in both newborns and children. The most common organism causing breast abscesses in this population is *Staphylococcus aureus*. Recently, an increasing number of skin and soft tissue abscesses caused by community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA and other variations) have occurred in children.

Treatment involves antibiotics, needle aspiration, or surgical drainage. The literature suggests that drainage alone, without adjunctive antibiotics, may be effective for skin and soft tissue abscesses caused by MRSA; no definitive antibiotic recommendation exists regarding MRSA

breast abscesses (60). If an incision and drainage-procedure is used, a circumareolar incision is recommended to avoid damage to the breast bud tissue, leading to later reduction in adult breast size; it is also important to avoid removing the entire breast bud, which can happen, if concern is raised about a "lesion" that may be the breast bud!

### **Post-pubertal infections: Lactational mastitis**

Breast infection or mastitis in the adolescent usually is noted during lactation, but also can be due to trauma (including sexual, areolar hair pulling [leading to a Montgomery tubercle abscess], squeezing an acne lesion, piercing), duct abnormality (as duct ectasia), or reduced immune defenses due to chronic illness (1,4,5,9). Mastitis develops to some degree in about 2% of pregnant women (lactational mastitis), usually in the postpartum period and less commonly, during pregnancy itself. Mastitis during lactation can be classified as an obstructive mastopathy, in which a major breast duct(s) becomes plugged leading to milk stasis, and secondary infection (due to *Staphylococcus aureus* [80%-90%], *Streptococcus pyogenes*, *Micrococcus pyogenes*, *Escherichia coli*, *Pseudomonas aeruginosa*, and others [as *Mycobacterium tuberculosis*]). Nipple trauma may also lead to infection. The same organism can be seen in the other, asymptomatic breast of the lactating female, as well as the pharynx of her infant. Milk from the infected breast may have an increased leukocyte count.

The infection usually develops with sudden onset of swelling, erythema, and tenderness; the skin is often warm to the touch in association with local cellulitis, regional lymphadenopathy, and if an abscess results, fluctuance develops. Extensive spread of the infection is usually limited by normal breast support tissue, including Cooper's ligaments; however, sometimes the support tissue can mask an abscess. Extensive breast tissue damage can result from large breast abscesses, usually developing in cases without proper management. The differential diagnosis of mastitis is listed in table 13. If mastitis does develop in an adolescent, pregnancy should be considered. Supportive laboratory studies include a needle aspiration with cultures, ultrasound, and possibly, blood cultures.

**Table 13. Differential diagnosis of breast mastitis**

Lactational mastitis
Non-lactational mastitis
Mondor's disease
Mammary duct ectasia
Recurrent subareolar abscess
Trauma (sexual and non-sexual)
Breast malignancy

Management of mastitis in cases of milk stasis (with no associated infection) is by the use of warm compresses and continued breast feeding, as well as pumping out extra-produced milk, until normal balance is established between production and consumption. Antibiotics are used in cases of infection in order to cover the expected bacteria that are seen in such infections (1,2,4,5,9). A variety of antibiotics have been used for 2 to 6 weeks, including amoxicillin, amoxicillin-clavulanic acid, erythromycin, B-lactamase-stable penicillin [i.e., dicloxacillin], or a cephalosporin (i.e., cephadrine or cephalexin); if fluctuance develops, incision and drainage of the abscess is necessary, using a circumareolar incision; the clinician should be suspicious of an abscess if antibiotics do not improve the initial infection (5,60). Antibiotics (sometimes given intravenously) are continued until the infection is resolved, including resolution of the pain and cellulitis. If outpatient treatment with these antibiotics are not helpful, consider the possibility of an abscess and use metronidazole or intravenous vancomycin (or other antibiotics) (61). Complications include recurrence (50% in a breast abscess), breast necrosis or scarring [sometimes mistaken for a fibroadenoma], and in rare cases, septicemia. Breast feeding is continued unless purulent discharge develops. Ultrasonography can successfully help evaluate follow-up results.

### **Non-lactational-nonpuerperal mastitis**

Non-puerperal mastitis is rare and its cause not known (see figures 30 and 31); its presentation is similar to that of lactational mastitis. There

may be known precipitating factors, such as trauma (including sexual foreplay and nipple piercing), duct ectasia, epidermal cysts, local skin infections, cystic breast disease, abscess of the Montgomery's glands or other sebaceous glands, syphilitic chancre or gumma, tuberculosis, Wegener's granulomatosis, fungal infections, and protozoan infections.

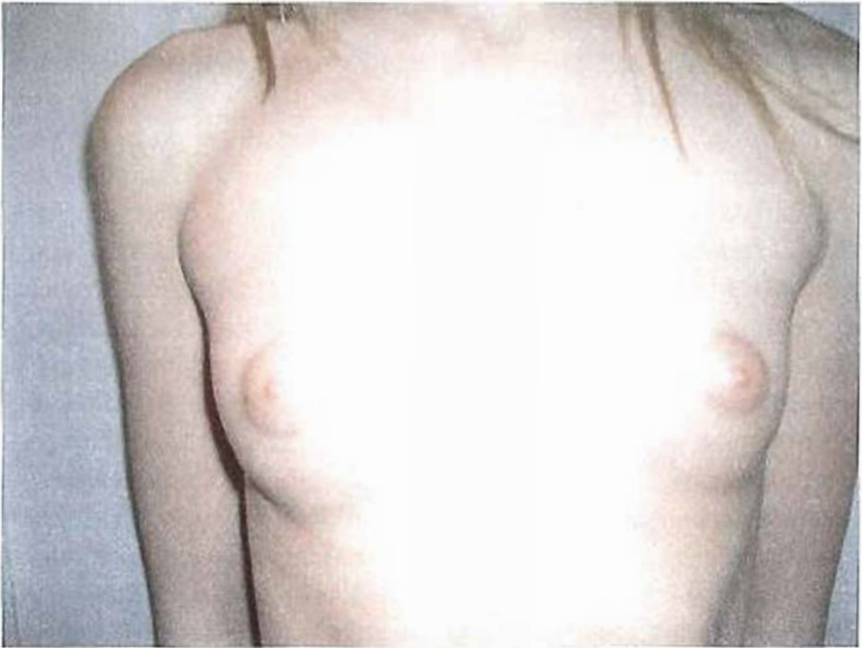


Figure 30. Mastitis, Right Breast in a 12 year old girl.

Management of bacterial mastitis, as already noted, includes warm compresses, antibiotic coverage, and sometimes, surgical drainage of the abscess. Table 13 reviews the differential diagnosis of mastitis, including Mondor's disease, a usually benign condition characterized by superficial phlebitis in the breast skin; it typically develops after trauma (such as a biopsy or sports trauma), though sometimes the precipitating event is not identified. Mondor's disease presents with tender cords of inflamed veins that can be palpated, and usually resolves spontaneously, with or without mild analgesics (62).



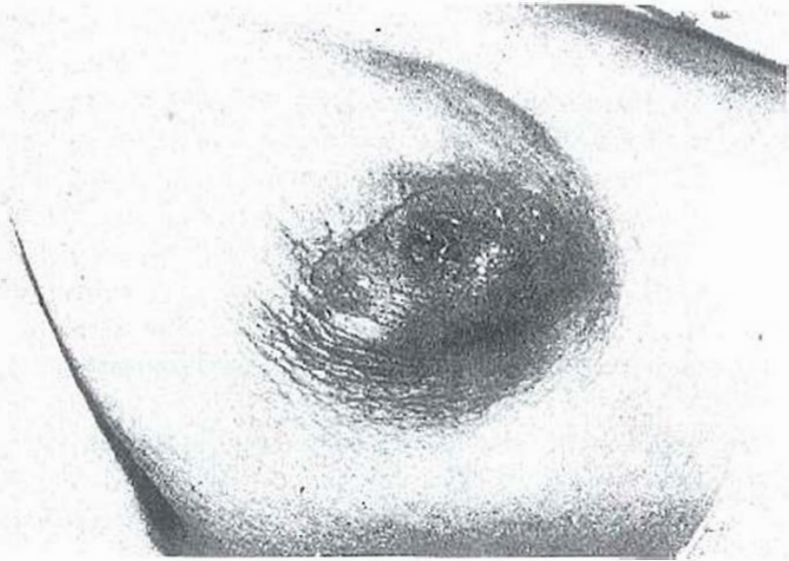


Figure 31. Staphylococcal Breast Abscess.

Body piercing in general has become more common in both female and male adolescents over the past decade. Cases of nipple piercing as the cause of local infection and disfiguration have been reported (4). Staphylococcus and Streptococcus species are the common causative organisms in these situations, but cases of Mycobacterium have also been noted. Treatment includes appropriate antibiotics and removal of the foreign body.

## SPORTS-INDUCED BREAST TRAUMA

### Nipple trauma

The nipple is a common site of injury, especially in female athletes, because it is the most prominent part of the breast (1,2,63,64). Coarse clothing (such as tight-fitting brassieres or shirts) can lead to an acute or chronic abrasive injury to the nipple, particularly during jogging or other actions, resulting in strong, repetitive nipple nibbling. It has been called jogger's nipple or bicyclist's nipple, the latter described in bicycle athletes who ride in cold wind and develop a raw, painful, bleeding

nipple (s). Cold exposure or direct nipple stimulation affects local nipple muscle fibers, inducing an erect, prominent nipple. There is a 20: 1 ratio of males to females with nipple injury in long-distance runners. The differential diagnosis of such nipple disease includes sports-induced trauma, intraductal papilloma, and carcinoma. Sports-induced nipple injury is assessed with prevention of further nipple trauma and treatment of any secondary infection. Prevention of nipple injury during exercise or sports is listed in table 14.

**Table 14. Prevention of sports-induced nipple injury\***

- |   |
|---|
| <ol style="list-style-type: none"> <li>1. Use a plastic bandage (ie, a Band-Aid) or petroleum jelly (Vaseline) before and during the exercise</li> <li>2. Use a properly fitted sports brassiere</li> <li>3. Avoid exposure to cold temperatures</li> <li>4. Use wind breaking material over the chest</li> <li>5. Special attention during pregnancy, when nipples are more prominent</li> </ol> |
|---|

\*Used with permission from: Greydanus DE, Patel DR: The female athlete: Before and beyond Puberty. *Pediatr Clin North Am* 2002;49:553-80.

## Breast trauma

Though fortunately not a common occurrence, sports-induced trauma to the breasts can occur, leading to breast contusions, lacerations or hematomas (63,64). Trauma often may occur during sports activity such as basketball or volleyball, but are noted in other sports as well. Contusions are due to superficial capillary rupture with ecchymosis along with edema, are usually mild, and may take up to three weeks to resolve. Abrasions result from various sports-related trauma, such as bicycle accidents (i.e., road racing, mountain biking), rodeo events, sliding, or baseball (i.e., from sliding). Parts of the female's bra may induce injury because of bra clips, underwire metal hooks, clips or straps. Lacerations may occur as well, and proper closure is important; observing for the development of a secondary abscess that can be painful is also part of the evaluation and follow-up.

Hematomas can develop from a strong blow to the breast that causes bleeding from blood vessels deep in the breast tissue. Fat necrosis may later develop with secondary induration, scarring, and calcification lasting for many years and being confused with breast carcinoma. Fortunately, most breast hematomas resolve spontaneously, though some require surgical aspiration. Table 15 reviews basic management of these trauma-induced breast injuries. Sports-induced injuries can be reduced with the use of a properly fitting sports brassiere. This should be especially designed for athlete use and is made of cotton material; regular replacement is important, no later than every 6 months.

**Table 15. Management of trauma-induced breast injuries\***

**1. Contusion**

- a. Application of cold (ice) every 15-20 minutes--several hours; do not apply ice directly to the skin but with a protective barrier.
- b. Appropriate analgesia
- c. Firm support

**2. Abrasion**

- a. Direct pressure to control bleeding
- b. Suturing may be necessary

**3. Laceration**

- a. Close with steri-strips or sutures
- b. Use good hygiene principles
- c. Apply a firm post-closure dressing
- d. Advice for the use of a supportive (sports) brassiere (including at night)
- e. Pain and swelling can be reduced with a cold pack
- f. Provide a tetanus toxoid if warranted
- g. Antibiotics may be needed, depending on the situation

**4. Hematoma**

- a. Most resolve without treatment
- b. Surgical aspiration may be necessary

\*Used with permission from: Greydanus DE, Patel DR: The female athlete: Before and beyond puberty. *Pediatr Clin North Am* 2002;49:553-80.

## BENIGN BREAST DISEASE

Breast tissue is made up of epithelium, adipose tissue, and connective tissue. Breasts can normally be nodular during the childbearing years, with considerable cyclic volume changes, as much as 50% during a menstrual cycle. The adolescent is at the beginning of breast changes that will continue over several decades and there can be some confusion between normal changes on the one hand, and benign breast disease on the other (1,2,9). Cyclic changes in the breast that reflect physiologic changes are normal and should not be labelled as a disease state. Thus, there can be a variety of changes, including physiologic (cyclic) swelling and tenderness (possibly part of PMT/ PMS), nodularity or significant lumpiness (cyclic or noncyclic), mastalgia (cyclic or noncyclic), and various dominant breast cysts or lesions (1,2,9,14,22,65-71).

Benign single or multiple cysts are noted in adolescents, though not as commonly as a fibroadenoma is noted in adolescent females. These benign cysts are typically not fixed to breast tissue and contain different amounts of sterile fluid that can be clear, brownish, or blood-tinged. Table 16 provides a partial classification of these benign cysts. A solitary large cyst (macrocyt or "blue-domed cyst") contains fluid with various colors (green, yellow, or black) that can be confused with a fibroadenoma or breast cancer; it is usually fluctuant, but can be hard or tense. Fine-needle aspiration (FNA) with cytology reveals the benign nature of the cyst and usually there is no recurrence (68,69).

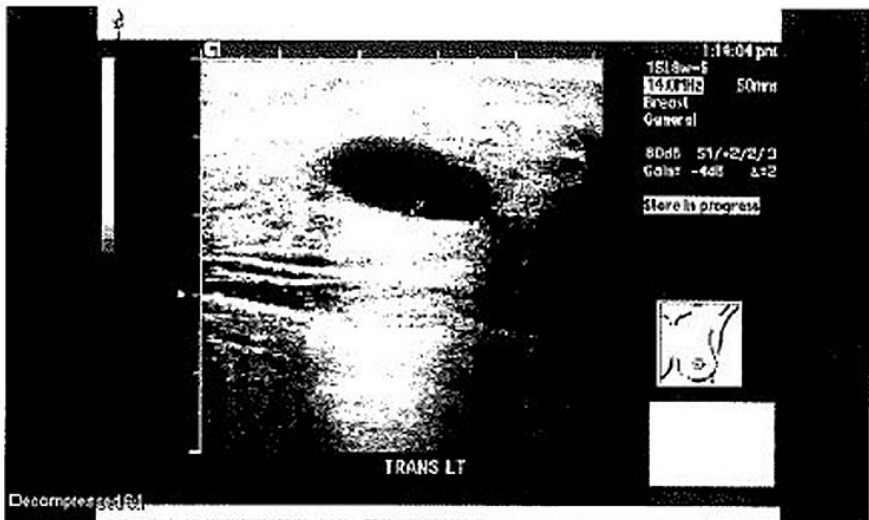
**Table 16. Types of benign breast cysts**

Fibrocystic change
Solitary large ("blue-domed") cysts
Simple single cyst
Galactocele
Pseudolumps (normal physiologic changes)
Traumatic fat necrosis
Others

During lactation, galactocele(s) can develop from overdistention of lactiferous duct(s), usually presenting as a subareolar mass with a yellow

discharge. The mass is excised if it does not disappear with continued lactation. Trauma to the breast can lead to the appearance of areas of fat necrosis in the breast.

A fine-needle aspiration of a cyst can be done testing for the presence of red blood cells (with a guaiac test) and abnormal cells (Papanicolaou fixative for cytology). If the mass disappears after aspiration, it is usually called a cyst and reexamination occurs in 2 to 3 months. If the mass reoccurs (as noted in as many as 50%), ultrasound imaging can be obtained, as well as ultrasonically-guided aspiration with a pneumocystogram to evaluate the cyst walls (70). Air can be injected into the cyst wall to decrease the risk of cyst recurrence. If the aspiration is non-diagnostic or possible, an excisional (open) biopsy can then be done under local or general anesthesia, in order to obtain more information about the lesion. Figure 32 shows the ultrasound image of a benign breast cyst, figure 33 reveals the ultrasound image of a breast hemangioma, and figure 34 notes a "breast lesion" that was actually an axillary node.



Used with permission from Kathleen Gadwood, MD, Ultrasound Division, Radiology Department, Bronson Hospital, Kalamazoo, Michigan .

Figure 32. Ultrasound: Benign Breast Cyst. In the medial upper left breast. There is a simple 1.2 x 0.7 x 1.1 cm cyst. Scanning also reveals a cyst at about 12:00 position in the left breast measuring 2.3 x 0.9 x 2.1 cm.



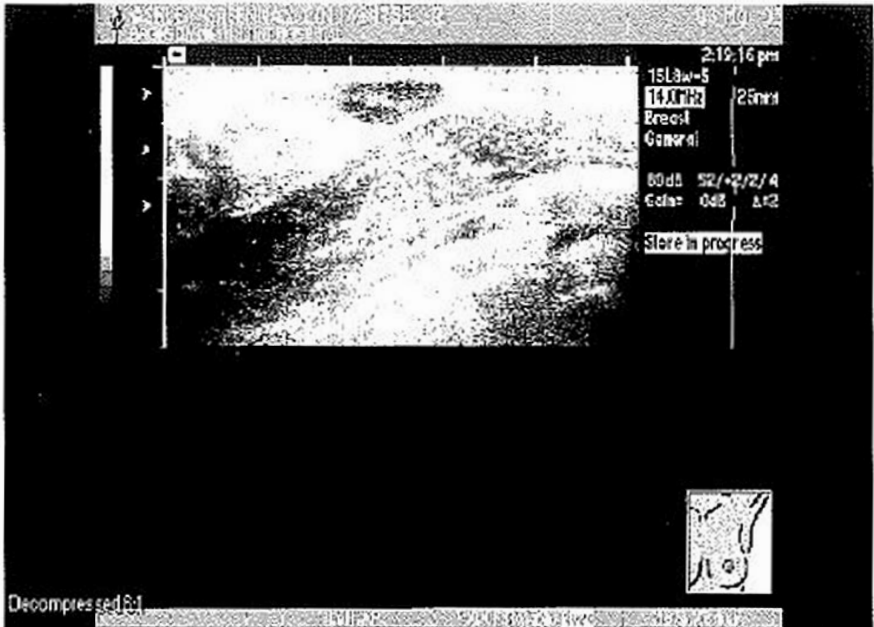
Used with permission from Kathleen Gadwood, MD, Ultrasound Division, Radiology Department, Bronson Hospital, Kalamazoo, Michigan.

Figure 33. Ultrasound: Left Breast. Mass, 3-month-old. On Visual inspection, there is swelling of the tissues involving the left breast area. This feels soft on palpation. There is a bluish discoloration through the skin. Ultrasound scanning targeted here shows a hypoechoic mound-shaped area of tissue behind the areola, without discrete borders. Color Doppler readily demonstrates multiple blood vessels composing this mass. The vessels represent a combination of arteries and veins. The bulk of the soft tissue swelling seems to be caused by enlarged vessels. There are no other nonvascular spaces to suggest lymphatic tissue. This does not have the appearance of gynecomastia. Impression: Left breast mass is consistent with hemangioma or other vascular malformation. This does not look like a lymphangioma or soft tissue mass from a neoplasm.

### Fibrocystic change

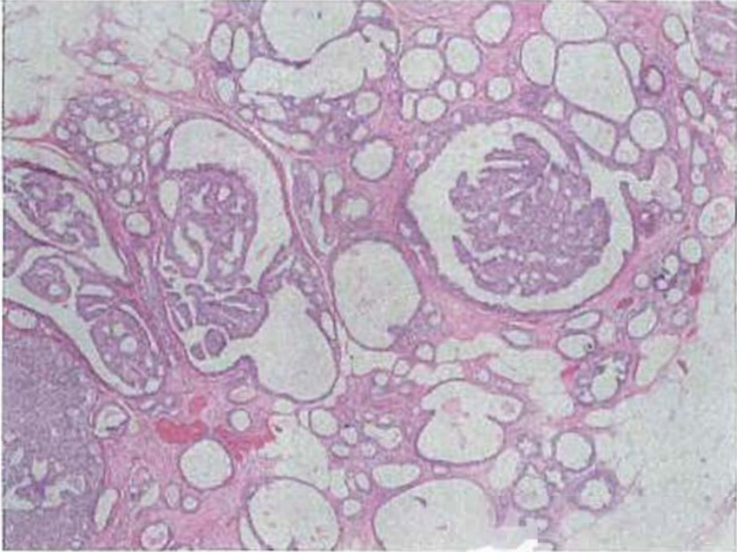
Formerly called fibrocystic disease, the term fibrocystic change is used to refer to hormonal-induced breast changes that are more physiologic in nature than overt disease. Though more common in females in their third decade of life and beyond, adolescent females may present with various degrees of breast tenderness and nodularity that

tends to change over the course of the menstrual cycle. Diffuse cord-like thickenings and lumps may develop over time, while some patients present with vague lumps or nodules (1,2,9,22). The second most common breast lesion in adolescents after the fibroadenoma is fibrocystic change (72). The etiology is unclear and often linked to estrogen and progesterone imbalances. Biopsy of these lesions reveals alveoli and terminal ducts with secretory material that are the basis of cystic development (57) (see figures 35-37). Some forms of benign breast disease (as cystic disease, atypical ductal or lobular hyperplasia, proliferative changes, others) are listed as risk factors for later breast cancer in the adult years (4,17,72,73).



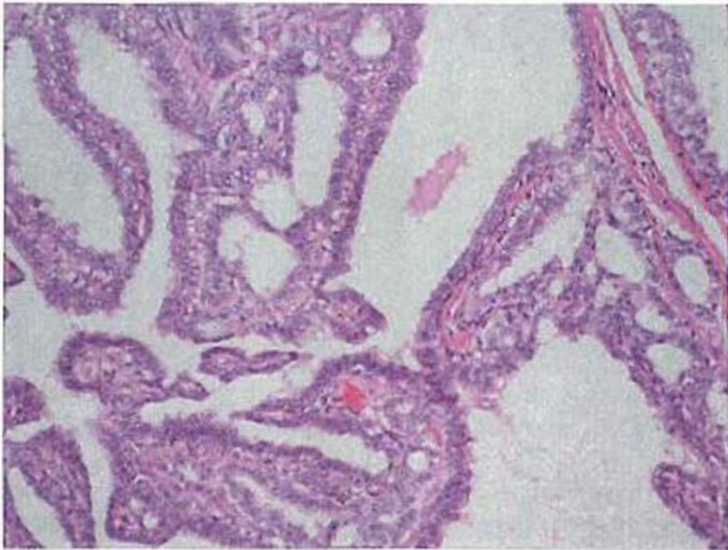
Used with permission from Kathleen Gadwood, MD, Ultrasound Division, Radiology Department, Bronson Hospital, Kalamazoo, Michigan.

Figure 34. Left Breast Lump. Scanning of the left breast lump (upper outer aspect of breast) demonstrates a 1.2 x 0.5 x 1 cm lymph node. Vascular hilum noted. No other suspicious findings are noted. Impression: Approximately 12 x 5 x 11 mm lymph node that corresponds to the left breast palpable finding.



Used with permission from Jeffrey Pearson, MD. Medical Director, Pathology Department, Bronson Hospital, Kalamazoo, Michigan.

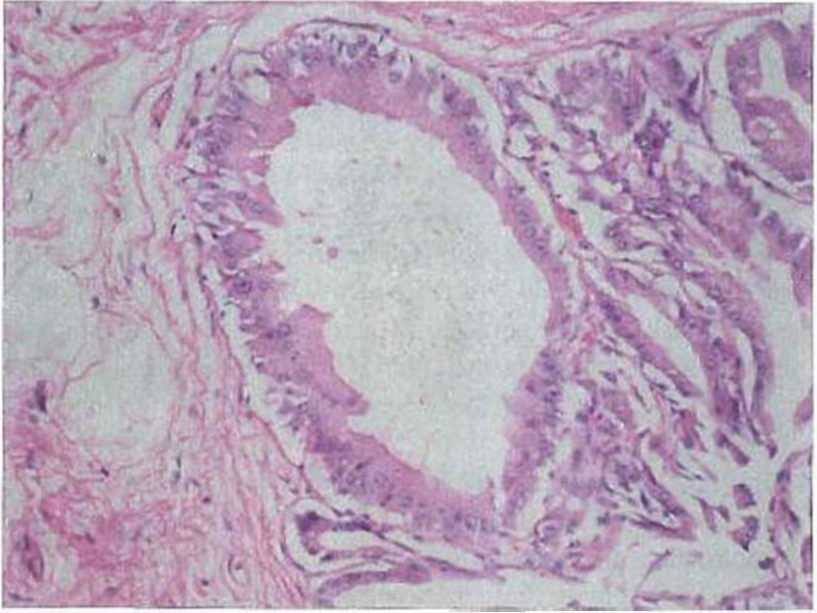
Figure 35. Fibrocystic Change Histology.



Used with permission from Jeffrey Pearson, MD, Medical Director, Pathology Department, Bronson Hospital, Kalamazoo, Michigan.

Figure 36. Fibrocystic Change Histology.





Used with permission from Jeffrey Pearson, MD. Medical Director, Pathology Department Bronson Hospital, Kalamazoo, Michigan.

Figure 37. Fibrocystic Change Histology.

Management depends on the severity of the condition and starts with reassurance of its benign nature, use of a well-fitting (sports) brassiere to prevent inflammation as well as stretching of breast ligaments, cold compresses, and a trial of mild analgesics (such as ibuprofen (other non-steroidal anti-inflammatory drugs) or acetaminophen). In more severe conditions, oral contraceptives are beneficial in as many as 90% of patients, by reducing overt cystic breast production. Some medications have been used to manage fibrocystic change in adult women and include danazol, bromocriptine, and tamoxifen. These drugs have no proven value in adolescent females and introduce possible adverse effects, including teratogenicity and masculinization. Primrose oil may be beneficial at 3 to 4 grams per day (72). There is also no proven value for anecdotal management such as limiting methylxanthine (caffeine) ingestion or adding such substances as vitamin E or calcium (72).

## **Breast pain (mastodynia; mastalgia)**

Mastodynia often refers to breast pain that develops as part of physiologic swelling and nodularity of breast tissue occurring on a cyclic or non-cyclic basis (1,2,4,9,14,22,57,74,75). It may develop or worsen 18 to 24 months after menarche and may, in some cases, be associated with episodes of breast hyperplasia (mammary dysplasia). Breast pain is observed in as many as 40% of reproductive age females and nearly 10% have their daily activity affected as a result (57). It may be part of a premenstrual tension syndrome (PMS), fibrocystic change, or related to such precipitants as pregnancy, infection, trauma, or medications (including oral contraceptives or other oral estrogen administration, phenothiazines, marijuana, others). Drugs that can lead to galactorrhea or gynecomastia can also cause breast pain (57). It is also important to rule out other causes that may be confused with breast pain, such as chest wall pain (Tietze syndrome or osteochondritis), cervical spine disease, cardiac disease or others (1,2,9,22). Thus, a careful assessment is necessary to identify the underlying cause of the pain.

Management of breast pain depends on its etiologic process (66). Mastalgia that seems to be related to menstrual cycle changes is usually mild and reassurance of its benign nature may be all that is necessary along with firm brassiere support and possibly the use of mild analgesics. Underlying precipitating factors, such as marijuana or other drug use, should be eliminated. Oral contraceptives may improve (or worsen) breast pain and some females report anecdotal improvement with avoidance of methylxanthines (i.e., caffeine in cola, tea, coffee), chocolate, and dairy products.

The addition of evening primrose oil ( $\gamma$ -linolenic acid) capsules (3 grams per day) is noted to help some females with cyclic mastalgia [61]. Vitamin E supplementation (600 IU per day of alpha-tocopherol) has anecdotal but no research-based support for improvement. Chasteberry is the fruit of the chasteberry tree that is found in western Asia, southwest Europe, and the southeastern United States. Chasteberry has been used for over many centuries for relief of various gynecologic symptoms and some authors note improvement in breast pain from taking chasteberry (76,77).

Some investigators have reported on the use of mastodinon for mild mastalgia and PMS (78). Danocrine is an anti-gonadotropin agent that is used by some clinicians to manage adult women with severe mastalgia; it has no proven benefit in adolescent females and its administration presents a number of potential severe adverse reactions, including teratogenicity, androgenization (with hirsutism), acne, weight gain, and others. Clinicians should always remember the classic dictum, *primum non nocere* (first, do no harm!).

## GYNECOMASTIA

Visible or palpable mammary gland development in males is called gynecomastia, a term introduced by the famous physician, Galen, in the 2nd century AD (4,14,79-81). In the newborn male it is called neonatal breast hypertrophy, as reviewed earlier. In prepubertal or pubertal gynecomastia, the subareolar enlargement is noticed starting at a diameter of 1 1/2 or 2 cm and usually reaches 3 cm, though much larger growth may occur; it can be unilateral, bilateral and/or familial. The tissue is usually firm, though it may blend into the surrounding tissue making differentiation from adipose tissue difficult. Gynecomastia is found in as many as two-thirds of males between Tanner Stage 2 and 4, usually beginning as a unilateral condition that eventually becomes bilateral. The breast swelling is often painful at presentation, and some youth complain of chest discomfort that may interfere with sports activity, including the development of nipple irritation (Jogger's Nipple) (63,64). The etiology is usually postulated as an imbalance between estrogen and androgen along with issues involving end-organ response to hormonal changes. Histology reveals a pattern of connective tissue stroma with infrequent lactiferous duct tubules.

Most cases of gynecomastia in young adolescent males are termed physiologic or idiopathic and resolve within 6 to 18 months (sometimes 2 years) (see figure 38). The evaluation should rule out pseudogynecomastia (i.e., appearance of breast enlargement that is really due to muscle development or obesity) and organic causes, as noted in table 17. Clinicians should be especially concerned about the development of breasts in males apart from Tanner stage 2 to 4 time period or if other

problems are noted, such as history of estrogen ingestion, finding of small testicles, and others, as noted in table 18 (see figure 39). Breast manipulation may lead to galactorrhea. Breast cancer is very rare in males; however, there is an increased risk of breast cancer in those with Klinefelter syndrome and those with a familial history of BRCA-2 mutations (2,56). There is also an increased incidence of prostate cancer in those with a history of BRCA-1 mutation (see figure 40).

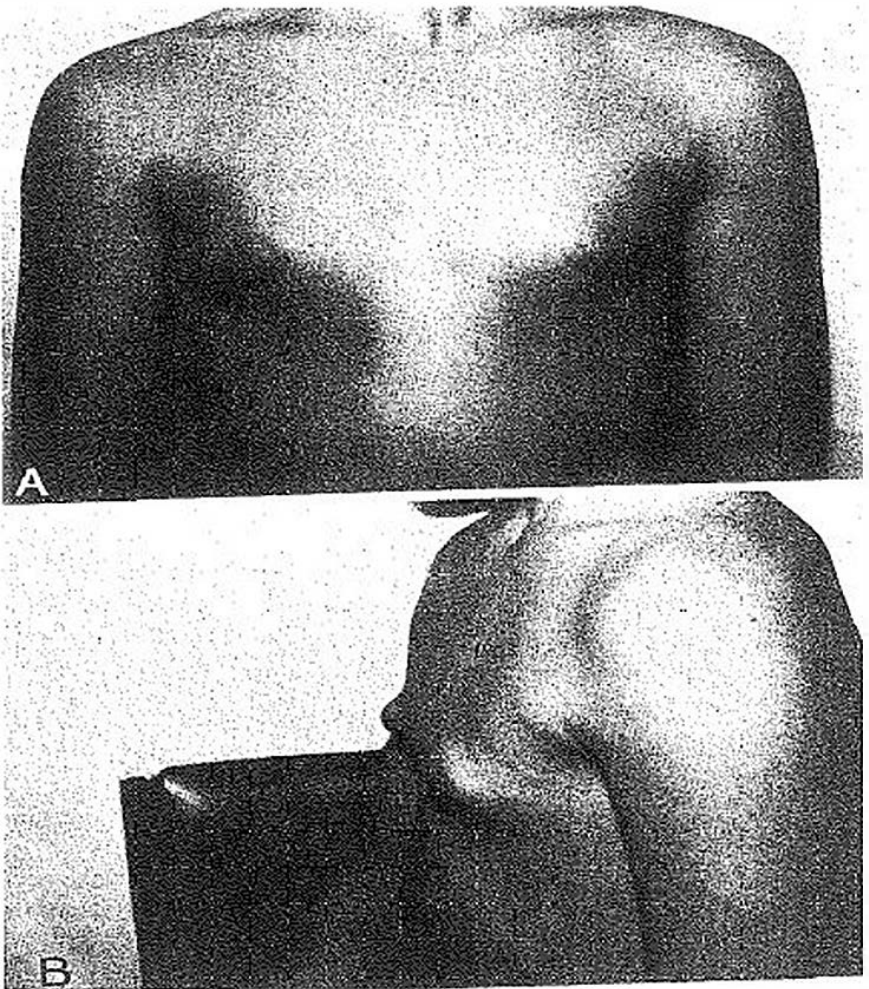


Figure 38. Gynecomastia in an Adolescent. B. Lateral View.

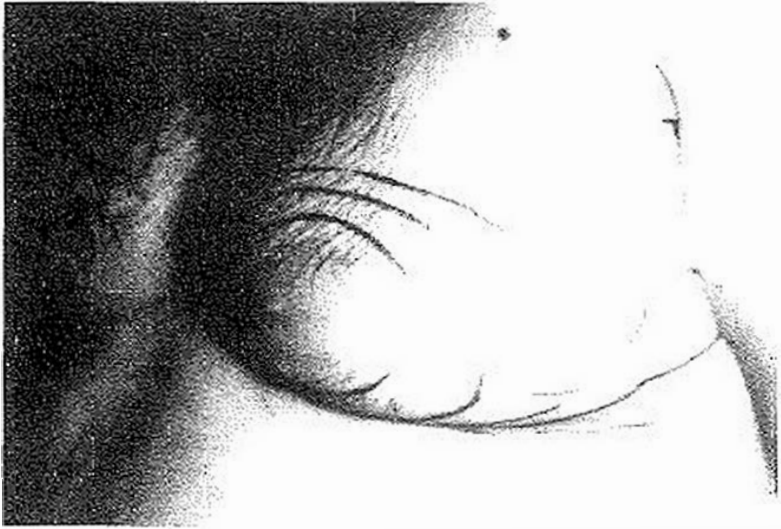
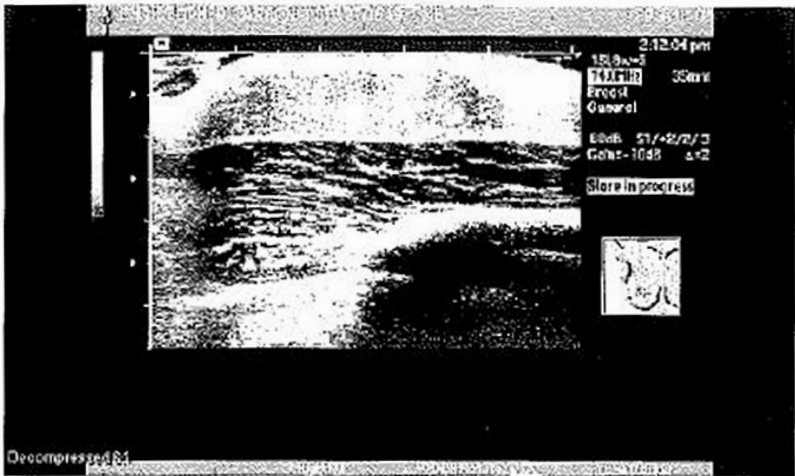


Figure 39. Gynecomastia in an Adult



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figure40. Breast Ultrasound. History of right nipple/subareolar enlargement, renal failure on dialysis, and hypertension in a 16 year old male. Ultrasound scanning shows an oval mound of uniform tissue in the right subareolar area which measures 3.3 by 3.6 by 0.9 cm. This seems to be: some focal glandular tissue. It is larger than on the left side, where the tissue measures 2.2 by 2.2 by 0.5 cm. There is no abnormal mass, no cystic change. Impression: The palpable fullness on the right is consistent with gynecomastia.

**Table 17. Causes of type II gynecomastia\***

Idiopathic	Miscellaneous drugs
Familial	Amphetamines
Associated with anosmia and testicular atrophy	Anabolic steroids
Reifenstein's syndrome	Birth control pills
Associated with hypogonadism and a small penis	Busulfan (and other chemotherapeutic agents)
Others	
Klinefelter syndrome	
Male pseudohermaphroditism	Cimetidine
Androgen insensitivity syndrome (Testicular feminization syndrome)	Clomiphene
Tumors (seminoma, Leydig cell tumor, teratoma, feminizing adrenal tumor, hepatoma, bronchogenic carcinoma)	Corticosteroids
	Digicatis
	Etretinate
	Estrogens
Leukemia	Human chorionic gonadotropin
Hemophilia	
Leprosy	Insulin
Thyroid dysfunction (hyper- and hypothyroidism)	Isoniazid (and other antituberculosis drugs)
Cirrhosis of the liver	
Traumatic paraplegia	
Chronic glomerulonephritis	Ketoconazole
Starvation (on refeeding)	Marijuana
	Methadone
	Reserpine
	Spirolactone
	Testosterone
	Tricyclic antidepressants
	Others

\*Used with permission from: Greydanus DE, Parks D, Farrell E. Disorders of the breasts in children and adolescents. *Pediatr Clin North Am* 1989;36(3):634.

**Table 18. Evaluation of gynecomastia**

History
Timing of breast appearance
Family history
Systemic disease history
Weight changes
Use of drugs or medications
Physical Examination
Vital signs (height, weight, blood pressure)
Breast development (Tanner Stage and breast size)
Genitals (Tanner Stage and any abnormality of the genitals)
Neurologic examination.
Laboratory Studies (Serum)
LH,FSH
Testosterone (free, total)
Estradiol
SHBG (sex hormone binding globulin)
HCG
17-urinary ketosteroids
DHBA-S
Androstenedione
Prolactin
Karyotype
Others

Management of idiopathic gynecomastia with breasts under 3 cm is usually reassurance that it is a "normal" occurrence, with further reassurance that he is not "feminine" or "turning into a female," and watchful waiting while the breast tissue resolves. If he is obese, measures for weight reduction may be helpful as well. Medications used for some adults with gynecomastia (i.e., antigonadotrophic agents [danazol], estrogen antagonists [clomiphene, toremifene], or aromatase inhibitors [testolactone]) are not recommended for adolescents since they have no proven efficacy, have potentially serious side effects, and the breast development returns when the drug is stopped. Underlying disorders

should be treated, as for example, testosterone replacement for a youth with small testes due to Klinefelter Syndrome.

Large breasts (Tanner Stage 3 or 4 as well as over 4 cm) are unlikely to fully resolve spontaneously. After two years of any size breasts, resolution is unusual because of the development of stromal fibrous tissue (57). Thus, the patient can be managed with surgery (i.e., periareolar incision and suction lipectomy or reduction mammoplasty) (4). Even males with small breasts may have severe emotional reactions to their breast development and should be offered surgery if necessary.

## NIPPLE DISCHARGE

Nipple discharge can be caused by many factors and disorders, as listed in table 19; the basic categories of etiologies are idiopathic, drug-induced, neurogenic, and endocrine/hormonal (including hypothalamic and pituitary disorders) (1,2,4,9,14,22,57,82-84). The evaluation of nipple discharge looks at the nipple secretion (color and amount), history of trauma (including breast manipulation), breast disorders, or menstrual abnormalities. The physical examination in a female with nipple discharge involves a careful breast examination, including nipple palpation. A ductogram (galactography) may be helpful in identifying underlying pathology, while surgery may be necessary to pinpoint the etiology of a breast lesion or remove an offending breast duct. Apocrine chromhidrosis refers to colored sweat secretion by periareolar apocrine glands.

**Table 19. Causes of nipple discharge**

- |                                  |
|----------------------------------|
| 1. Milky discharge               |
| a. Lactation                     |
| b. Breast cancer                 |
| c. Phenothiazine                 |
| d. Pituitary microadenoma        |
| e. Elevated TSH (hypothyroidism) |
| f. Acromegaly                    |



2. Yellow discharge
  - a Galactocele
  - b Physiologic effects
3. Serous, clear or greenish discharge: Physiologic Breast Cyst
4. Bloody discharge
  - a Cystic ductal hyperplasia
  - b Intraductal papilloma
  - c Cystosarcoma phyllodes
  - d Papillary carcinoma
5. Brownish discharge
  - a Montgomery's gland secretion
  - b Intraductal papilloma
- 6 Purulent discharge: mastitis or breast abscess

## GALACTORRHEA

Galactorrhea refers to breast milk secretion apart from birth or abortion and the fluid may be white (milky), but also clear, green, or yellow. The discharge can be minimal or copious and a Sudan stain reveals the presence of fat globules in the discharge. Table 20 lists various causes of galactorrhea, though the most frequent factors are idiopathic (benign galactorrhea), suckling, self-manipulation, pharmacologic, pituitary prolactinoma, and hypothyroidism (1,2,82). A pregnancy-related rise in prolactin levels can lead to a persistent state after a therapeutic abortion, delivery without nursing, or miscarriage. Idiopathic or benign galactorrhea refers to an end-organ hypersensitivity to normal prolactin levels. One cause of hyperprolactinemia is macroprolactinemia with elevated amounts of prolactin molecules that are larger than normal prolactin molecules, just as immunologically active, but not as biologically active; it represents a benign biochemical condition.

**Table 20. Causes of galactorrhea\***

Pregnancy, Lactation

Stress. Exercise

Recent Pregnancy Terminated by Spontaneous or Induced Abortion

**Neurogenic**

Chest wall disorders

Bronchiectasis and chronic bronchitis

Herpes zoster

Chronic crutch use

Thoracotomy or thoracoplasty

Burns to chest wall

Breast (nipple) manipulation or stimulation (sexual

foreplay)

Chronic inflammatory disease or abscess of breast

Psychogenic, including pseudocyesis and pseudonursing

Miscellaneous

Hysterectomy or uterine tumors

Laparotomy

Spinal cord disorders and surgery

Idiopathic normoprolactinemia, with or without

amenorrhea

**Central nervous system abnormalities**

Diffuse brain disease

Coma

Pseudotumor cerebri

Encephalitis and sequelae

Uremia

Tumors, infiltrations, structural abnormalities

Neurocutaneous syndromes

Craniopharyngioma

Pineal tumors

Other intracranial tumors, cysts, and masses

Histiocytosis X

Sarcoidosis

Pituitary

Stalk section

Empty sella syndrome  
Pituitary infarction and Sheehan syndrome  
Hyperprolactinemia with or without prolactinoma  
Other functional pituitary tumors

**Miscellaneous**

Hypothyroidism and hyperthyroidism  
Hypogonadism  
Adrenal tumors and hypernephromas  
Nelson syndrome  
Testicular and ovarian tumors  
Polycystic ovary syndrome (PCOS)  
Starvation or refeeding (including anorexia nervosa)  
Cushing disease  
Chronic renal disease  
Cirrhosis  
Acute intermittent porphyria  
Oral Contraceptive pills  
Monoamine oxidase inhibitors  
Amphetamines  
Chlordiazepoxide  
Meprobrunate  
Metoclopramide  
Bromocriptine withdrawal  
Cimetidine and ranitidine  
Tamoxifen  
Verapamil  
Isoniazid  
Estrogens  
Opiates (including codeine and heroin)  
Phenothiazines, thioxanthenes, other psychotropic drugs  
Tricyclic antidepressants  
Other chemotherapy drugs (cisplatin, cytosine arabinoside, adriamycin)  
Others

- With permission from: Greydanus DE. Breast and gynecological disorders. In: Hofmann AD, Greydanus DE, eds. Adolescent medicine, 3<sup>rd</sup> ed. Stamford, CT: Appleton Lange, 1997:531.

A wide variety of pharmacologic agents can induce hyperprolactinemia due to underlying mechanisms as listed in table 21. Hyperprolactinemia can develop in adolescent males who were treated in childhood with chemotherapeutic agents (as doxorubicin, cytosine arabinoside, cisplatin) or with testicular radiation. Other pharmacologic agents include oral contraceptives (noted with taking or withdrawal), methyltestosterone, spironolactone, reserpine, and others. The relationship of heavy marijuana use and galactorrhea remains anecdotal and controversial. If an offending drug is stopped, galactorrhea usually resolves. Hyperprolactinemia may result from hypothyroidism (rarely hyperthyroidism), stress, depression, anxiety, hypothalamic injury (surgery, tumor, infection), exercise, intercostal nerve stimulation, gonadal hypofunction, polycystic ovarian syndrome (PCOS) and other conditions noted in table 20. Moderate hyperprolactinemia (less than 1750 mU/L) can develop in hypothyroidism and polycystic ovarian syndrome (PCOS).

**Table 21. Mechanisms of drug-induced galactorrhea**

<b>Dopamine receptor blockers</b>
Phenothiazines
Butyrophenones
Tricyclic antidepressants
<b>Dopamine depletors</b>
Cocaine
<b>Lactotroph stimulators</b>
Verapamil
Narcotics (opiates)
High-dose estrogens
<b>Gastrointestinal dopamine antagonist</b>
Metoclopramide

Evaluation of galactorrhea depends on the findings of a careful history and physical examination (1,2). A cytologic evaluation of the discharge fluid can be performed along with serum gonadotropins, prolactin, thyroid screen, and a head MRI or CT. Management of galactorrhea depends on the underlying factor(s). If there is an offending

drug, it should be stopped, as should breast manipulation if causative. Any thyroid dysfunction should be identified and corrected.

Most pituitary prolactinomas produce prolactin levels of 80 to 200 ng/ml or higher. The spectrum of this lesion ranges from a microadenoma (3-10 mm mass) to a macroadenoma (10 mm or more in diameter) with sella turcica erosion and optic nerve impingement. A microadenoma can present with a stable, non-progressive clinical course in which serum prolactin (less than 3000 mU/L) is 2 to 10 times normal and symptoms include amenorrhea due to anovulation and galactorrhea. A macroadenoma may present with galactorrhea along with a variety of symptoms (see table 22); the prolactin level is very high at 8,000 mU/L or more. Visual field studies (looking for bitemporal hemianopsia) and a head CT/MRI may reveal the presence of a pituitary adenoma. Management of a pituitary adenoma depends on its size, but often a dopamine agonist is used, as bromocriptine, to remove the tumor if it is small enough; a macroadenoma may be reduced in size with a dopamine agonist followed by surgery (i.e., transsphenoidal resection) [85]. Other dopamine agonists include L-dopa and ergotamine.

**Table 22. Symptoms of pituitary microadenoma**

Menstrual change (Amenorrhea)
Headaches
Peripheral vision loss
Appetite changes
Abnormal sexual development
Polyuria, polyphagia, polydipsia
Infertility
Loss of libido
Impotence in males

## ACKNOWLEDGMENTS

This chapter is a revised version and adapted with permission from Greydanus DE, Matytsina L, Gains M. Breast disorders in children and adolescents. *Prim Care Clin Office Pract* 2006; 33:455-502.

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