

Gynecomastia

Background

Gynecomastia is a benign enlargement of the male breast resulting from a proliferation of the glandular component of the breast. Gynecomastia is defined clinically by the presence of a rubbery or firm mass extending concentrically from the nipples. Fat deposition without glandular proliferation is termed pseudogynecomastia. Although gynecomastia is usually bilateral, it can be unilateral.

Pathophysiology

Gynecomastia results from an altered estrogen-androgen balance, in favor of estrogen, or increased breast sensitivity to a normal circulating estrogen level. The imbalance is between the stimulatory effect of estrogen and the inhibitory effect of androgen. Estrogens induce ductal epithelial hyperplasia, ductal elongation and branching, proliferation of the periductal fibroblasts, and an increase in vascularity. The histologic picture is similar in male and female breast tissue after exposure to estrogen.

Estrogen production in males is mainly from the peripheral conversion of androgens (testosterone and androstenedione) through the action of the enzyme aromatase, mainly in muscle, skin, and adipose tissue in the forms of estrone and estradiol.

The normal production ratio of testosterone to estrogen is approximately 100:1. The normal ratio of testosterone to estrogen in the circulation is approximately 300:1.

Frequency

Gynecomastia is the most common cause for male breast evaluation. It is common in infancy, adolescence, and in middle-aged to older adult males. One estimate is that 60-90% of infants have transient gynecomastia due to the high estrogen state of pregnancy.

The next peak of occurrence is during puberty, with a prevalence ranging from 4-69%. Some reports have shown a transient increase in estradiol concentration at the onset of puberty in boys who develop gynecomastia. Pubertal gynecomastia usually has an onset in boys aged 10-12 years. It generally regresses within 18 months, and persistence is uncommon in men older than 17 years.

The third peak occurs in older men, with a prevalence of 24-65%. Gynecomastia in adults is often multifactorial. Increased aromatization of testosterone to Estradiol and the gradual decrease of testosterone production in the aging testes account for most adult men with gynecomastia. Older men are also more likely to take medications associated

with gynecomastia than are younger men. Recent estimates suggest the following etiologies in males seeking medical attention for gynecomastia:

- Persistent pubertal gynecomastia – 25%
- Drugs – 10-25%
- No detectable abnormality – 25%
- Cirrhosis or malnutrition – 8%
- Primary hypogonadism – 8%
- Testicular tumors – 3%
- Secondary hypogonadism – 2%
- Hyperthyroidism - 1.5%
- Chronic renal insufficiency – 1%

History

A thorough history is essential to evaluate the causes of gynecomastia.

- Note the age of onset and the duration.
- Ask about recent changes in the size of the nipples and the presence of pain or discharge from the nipples.
- Inquire if the patient has any history of mumps, trauma to the testicles, use of alcohol, or use of drugs (e.g., prescription medications, over-the-counter medications, and recreational drugs).
- Note any family history of gynecomastia.
- Evaluate the patient's history for sexual dysfunction, infertility, or Hypogonadism (impotence, decreased libido and strength).

Physical

- Perform a thorough examination of the breasts, noting their size and consistency. Also determine the presence of any nipple discharge or axillary lymphadenopathy.
- Differentiate between true gynecomastia and pseudogynecomastia/lipomastia. These 2 entities may be distinguished by having the patient lie on his back with his hands behind his head. The examiner then places his thumb on each side of the breast, and slowly brings them together. In true gynecomastia, a ridge of glandular tissue will be felt that is symmetrical to the nipple-areolar

complex. With pseudogynecomastia, the fingers won't meet until they reach the nipple.

- Gynecomastia can be detected when the size of the glandular tissue exceeds 0.5 cm in diameter.
- Examine the testicles, noting their size and consistency. Carefully look for the presence of nodules or asymmetry.
- Note signs of feminization, including typical body hair distribution and eunuchoid habitus.
- Check for any stigmata of chronic liver disease, thyroid disease, or renal disease.

Causes

Gynecomastia can be physiologic or pathologic.

- Physiologic gynecomastia is seen in newborn infants, pubescent adolescents, and elderly individuals.
- Pathologic gynecomastia can be caused by decreased production and/or action of testosterone, increased production and/or action of estrogen, or drug use; however, gynecomastia can also be idiopathic.
 - Conditions that result in primary or secondary hypogonadism and cause decreased production and/or action of testosterone include the following:
 - Klinefelter syndrome
 - Congenital anorchia
 - Testicular trauma
 - Testicular torsion
 - Viral orchitis
 - Kallmann syndrome
 - Pituitary tumors
 - Malignancies that increase the serum human chorionic gonadotropin (hCG) (eg, large cell lung cancer, gastric carcinoma, renal cell carcinoma, hepatoma)
 - Renal failure
 - Hyperthyroidism

- Malnutrition
- Androgen insensitivity syndrome
- Five alpha-reductase deficiency syndrome
- Increased production and/or action of estrogen can occur at the testicular level or at the periphery
- From the testes, which can be due to testicular tumors or to ectopic production of hCG as is reported with carcinoma of lung, kidney, GI tract, and extragonadal germ cell tumors
- From peripheral conversion, which can be due to increased substrate or increased activity of aromatase as in chronic liver disease, malnutrition, hyperthyroidism, adrenal tumors, and familial gynecomastia
- Various drugs are implicated in gynecomastia and can be classified into the following categories:
 - Estrogens or drugs with estrogen like activity such as diethylstilbestrol, digitalis, phytoestrogens, and estrogen-contaminated food and estrogen-containing cosmetics
 - Drugs that enhance estrogen synthesis such as gonadotropins, clomiphene, phenytoin, and exogenous testosterone
 - Drugs that inhibit testosterone synthesis or action such as ketoconazole, metronidazole, alkylating agents, cisplatin, spironolactone, cimetidine, flutamide, finasteride, and etomidate
 - Drugs that act by unknown mechanisms such as isonicotinic acid hydrazide, methyldopa, busulfan, tricyclic antidepressants, diazepam, penicillamine, omeprazole, phenothiazines, calcium channel blockers, ACE inhibitors, alcohol, marijuana, and heroin
 - Drugs in the same class do not all cause gynecomastia to the same extent

Differential

Breast Cancer
 Dermoid Cyst
 Hematoma
 Lipoma
 Lymphangioma
 Neurofibroma

Other Problems to be considered

Hypogonadism
Male sexual dysfunction

Lab Studies

- Patients with physiologic gynecomastia do not require further evaluation.
- Further evaluation is necessary in patients with the following:
 - Breast size greater than 5 cm (macromastia)
 - A lump that is tender, of recent onset, progressive, or of unknown duration
 - Signs of malignancy (e.g., hard or fixed lymph nodes or positive lymph node findings)
- A serum chemistry panel may be helpful in evaluating for renal or liver disease.
- A free or total testosterone, leuteinizing hormone (LH), estradiol, and dehydroepiandrosterone sulfate levels to evaluate a patient with possible feminization syndrome.
- Obtain thyroid-stimulating hormone (TSH) and free thyroxine levels if hyperthyroidism is suspected.

Imaging Studies

- Order a mammogram if one or more features of breast cancer are apparent upon clinical examination. This can be followed by fine-needle aspiration or breast biopsy, as the case merits.
- Obtain a testicular ultrasound if the serum estradiol level is elevated and the clinical examination findings suggest the possibility of a testicular neoplasm.

Other Tests

Asymptomatic and pubertal gynecomastia does not require further tests and should be reevaluated in 6 months

Medical Care

- Generally, no treatment is required for physiologic gynecomastia.

- A major factor that should influence the initial choice of therapy is the duration of gynecomastia. It is unlikely that any medical therapy will result in significant regression in the late fibrotic stage (a duration of 12 mo or greater). As a result, medical therapies, if used, should be tried early in the course.
- Pubertal gynecomastia resolves spontaneously within several weeks to 3 years in approximately 90% of patients. Breasts greater than 4 cm in diameter may not completely regress.
- Identifying and managing an underlying primary disorder often alleviates breast enlargement.
- If hypogonadism (primary or secondary) is the cause, parenteral or transdermal testosterone replacement therapy is instituted. Testosterone does have the potential of exacerbating the gynecomastia with the aromatization of the exogenous hormone into estradiol.
- For patients with idiopathic gynecomastia or residual gynecomastia after treatment of the primary cause, medical or surgical treatment may be considered.
- Clomiphene, an antiestrogen, can be administered on a trial basis at a dose of 50-100 mg per day for up to 6 months. Approximately 50% of patients achieve partial reduction in breast size, and approximately 20% of patients note complete resolution. Adverse effects, while rare, include visual problems, rash, and nausea.
- Tamoxifen, an estrogen antagonist, is effective for recent-onset and tender gynecomastia when used in doses of 10-20 mg twice a day. Up to 80% of patients report partial to complete resolution. Tamoxifen is typically used for 3 months before referral to a surgeon. Nausea and epigastric discomfort are the main adverse effects.
- Other drugs used less frequently include danazol and testolactone.
 - Danazol, a synthetic derivative of testosterone, inhibits pituitary secretion of LH and follicle-stimulating hormone (FSH), which decreases estrogen synthesis from the testicles. The dose used for gynecomastia is 200 mg twice a day. Complete resolution of breast enlargement has been reported in 23% of cases. Adverse effects include weight gain, acne, muscle cramps, fluid retention, nausea, and abnormal liver function test results.
 - Testolactone, a peripheral aromatase inhibitor, has been used with varying success rates in doses of 150 mg 3 times per day for 6 months. Nausea, vomiting, edema, and worsening of hypertension have been reported with its use.
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Surgical Care

- Reduction mammoplasty is considered for patients with macromastia or long-standing gynecomastia or in those in whom medical therapy failed. It is also considered for cosmetic reasons (and accompanying psychosocial reasons).
- If surgery is necessary for patients with lipomastia (ie, pseudogynecomastia), liposuction may be warranted.
- More extensive plastic surgery may be required in patients with marked gynecomastia or who have developed excessive sagging of the breast tissue that may occur with weight loss.
- Complications of surgery include sloughing of tissue due to compromised blood supply, contour irregularity, hematoma or seroma formation, and permanent numbness to the nipple-areolar area.

Complications

- Men with Klinefelter syndrome have a 10- to 20-fold increased risk for breast cancer.
- Other than the associated risk of breast cancer, gynecomastia does not cause any long-term complications.

Prognosis

- In approximately 90% of cases, pubertal gynecomastia usually resolves in months to several years.
- Gynecomastia secondary to an underlying treatable cause (eg, drug-induced gynecomastia) usually responds to treatment or removal of the primary cause.
- Macromastia seldom resolves completely and often requires surgery.

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