THE JOURNAL OF FAMILY PRACTICE

Gynecomastia: When is treatment indicated?

This algorithmic approach can simplify your clinical evaluation and help you decide whether intervention or watchful waiting is appropriate.

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The authors reported no potential conflict of interest relevant to this article.

PRACTICE RECOMMENDATIONS

› *Examine enlarged male breasts to differentiate between true gynecomastia and pseudogynecomastia (seen with obesity) or a mass suggestive of tumor activity.* (C)

› *Ask patients about the use of medications associated with gynecomastia, such as some antihypertensives, antibiotics, psychotropic agents, or hormones.* (C)

› *Order renal function tests and measure levels of liver enzymes, testosterone, and other hormones when initial history and examination findings are insufficient for a diagnosis.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶ Harry J is a 57-year-old man who came to us for evaluation and management of hypertension. He also complained of chronic headaches. Our initial examination revealed a body mass index (BMI) of 29 kg/m^2 and blood pressure (BP) of 150/100 mm Hg. The hypertension responded well to a combination of valsartan and hydrochlorothiazide. A few months later, he developed left breast soreness, as well as decreased libido. Examination revealed a round movable subareolar nodule 2 cm in diameter, with no associated skin changes or lymphadenopathy. Laboratory results were: total testosterone, 106 ng/dL (normal, 241-827); free testosterone, 23 pg/mL (47-244); thyroid-stimulating hormone (TSH), 2.222 mIU/mL (0.350-5.500); and prolactin, 102.7 ng/mL (2.1-17.7). Magnetic resonance imaging (MRI) of the brain revealed a nodular density <10 mm in the pituitary gland with minimal displacement of the stalk, consistent with a microadenoma.

Enlargement of the male breasts—gynecomastia—is caused by a benign proliferation of the ductal epithelium, due to a relative increase in the ratio of free estrogen to androgen locally in the breast. Gynecomastia of recent onset is often associated with pain and tenderness, as was the case with our patient.

Often self-limiting, age-related influences. Gynecomastia is common in newborns, during adolescence, and in old age.[1] In both male and female newborns, maternal and placental estrogens induce bilateral proliferation of breast tissue. This resolves within a few weeks after birth. During the early stages of male puberty, there is a relative increase in estrogens derived mostly from peripheral aromatization of testicular and adrenal androgens. If gynecomastia results, it usually regresses spontaneously as testicular testosterone production increases in late puberty.[2] Gynecomastia is also common in elderly men due to a decrease in testosterone production and an increase in sex hormone binding globu-

lin (SHBG) that lowers free testosterone levels.

Deleterious contributing factors. Several other potential causes of gynecomastia exist (**TABLE 1**),[3,4] and these can usually be identified with a systematic approach using a careful history, physical examination, and selected laboratory studies. Many medications are associated with gynecomastia (**TABLE 2**),[5] one of the most common being spironolactone due to its antiandrogenic activity at the receptor level.[5] Some drugs, although associated with gynecomastia, cannot be linked to a direct cause-and-effect mechanism. These factors are compounded in elderly, obese men who take medications such as spironolactone, known to cause gynecomastia.

A patient's medical history may reveal chronic conditions associated with gynecomastia. Such disorders include cirrhosis, hyperthyroidism, malnutrition, and chronic kidney disease. Rarely, gynecomastia can be a manifestation of a testicular, adrenal, or other neoplasm.

Despite a thorough evaluation, no detectable abnormality is found initially in 25% of gynecomastia cases.[6] Close observation and monitoring is necessary in such instances, to ensure the earliest possible identification of the underlying cause and initiation of appropriate medical or surgical therapy.

Initially, gynecomastia has no discernible cause in 25% of cases.

First steps in the clinical evaluation

In cases of male breast enlargement, first determine whether you are dealing with true gynecomastia or "pseudogynecomastia," which involves increased fat deposits typically seen in obese individuals.[3] In cases of pseudogynecomastia, the tissue is uniformly enlarged and soft, with the same consistency as adipose tissue.

In about half of the cases of gynecomastia, the condition is bilateral.[3] It is characteristically a rubbery or firm mass concentric with the nipple-areolar complex.

Clues to look for in the history. When examination suggests true gynecomastia, conduct a focused history to determine if medications or other substances might be causing the problem. (See "A case where drug therapy was to blame" on page 722.) Some plant-derived oils used as skin care products have also been associated with gynecomastia due to weak estrogenic or anti-androgenic activity.[7]

The history may also uncover significant weight gain, because obesity is associated with increased aromatase activity resulting in a relative increase in estrogens systemically and locally in the breast. When obesity is the cause of gynecomastia, the breast exami-

TABLE 1
Causes of gynecomastia[3,4]

Physiologic
Neonatal
Adolescent
Aging-related
Drug induced
Antiandrogens
Antibiotics
Antihypertensive agents
GI agents
Hormones
Illicit drugs
Psychiatric drugs
Decreased androgen production
Primary (testicular) hypogonadism
Secondary (central) hypogonadism
Decreased androgen effect or synthesis
Androgen insensitivity syndrome
5α-Reductase deficiency
17-β-Hydroxysteroid dehydrogenase deficiency
Increased estrogen production
Adrenal tumor
Testicular tumor
hCG-secreting tumor
Familial aromatase excess syndrome
Other
Liver disease
Thyrotoxicosis
Obesity
Renal disease
Malnutrition

GI, gastrointestinal; hCG, human chorionic gonadotropin.

TABLE 2
Drugs associated with gynecomastia[5]

Antiandrogens	Bicalutamide, flutamide, finasteride, spironolactone
Antibiotics	Isoniazid, ketoconazole, metronidazole
Antihypertensive agents	Amlodipine, diltiazem, nifedipine, verapamil, captopril, enalapril
GI agents	Cimetidine, ranitidine, omeprazole
Hormones	Anabolic steroids, estrogens, hCG, growth hormone, GnRH agonists
Illicit drugs, alcohol	Marijuana, methadone
Psychiatric drugs	Psychotropic agents, tricyclic antidepressants
Other	Antiretroviral agents, digitalis, fibrates, methotrexate, statins

GI, gastrointestinal; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin.

nation reveals firm, rubbery tissue (unlike the findings in pseudogynecomastia, where there is a soft enlargement of the breast). Alternatively, a history of weight loss is important because it can lead to hypothalamic dysfunction and a decrease in gonadotropin (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) secretion, resulting in decreased testosterone levels.[8]

Also inquire about prior diagnoses of liver cirrhosis or thyrotoxicosis or the presence of symptoms suggestive of these disorders, such as fatigue, jaundice, bloating, heat intolerance, or heart palpitations. These conditions can alter the metabolism of sex steroids and their binding proteins. A history of decreased libido and erectile dysfunction is suggestive of low testosterone levels, also known as hypogonadism. Headaches, visual disturbances, and behavioral abnormalities suggest a hypothalamic or pituitary disorder resulting in decreased FSH and LH levels and secondary hypogonadism. A family history of gynecomastia is elicited in half the patients with persistent pubertal gynecomastia.[9]

Physical examination. For all patients (except newborns), calculate the BMI and measure arm span and upper and lower body segments. A eunuchoid proportion—arm span 2 cm or greater than height—is associated with early-onset hypogonadism that precedes fusion of the epiphyses.[3] Thus, you'll need to consider congenital disorders of the testes, such as Klinefelter syndrome, as well as hypothalamic or pituitary disease, such as Kallmann syndrome, resulting in deficient FSH and LH production.

As noted earlier, you'll need to examine the breasts to determine if true gynecomastia exists, as opposed to increased adipose tissue or the presence of a suspicious mass. A hard or irregular mass outside the areola, especially if associated with skin changes such as dimpling or retraction, should raise the possibility of breast carcinoma. Promptly arrange for diagnostic mammography and possible biopsy in this setting.

Carefully examine the secondary sexual characteristics, including body hair distribution and muscle mass. Inspect the external genitalia, penile development, and position of the urethral meatus. Note testicular size and consistency. Small, firm testes are suggestive of dysgenetic gonads found in patients with Klinefelter syndrome (47 XXY), whereas small, soft testes suggest secondary hypogonadism. A unilateral testicular mass raises suspicion of a neoplasm. Palpate the prostate in older men, especially if contemplating androgen therapy, which could exacerbate a preexisting focal prostate cancer.

Look for signs of hyperthyroidism, such as goiter, exophthalmos, tachycardia, and hyper-reflexia. Examine the abdomen for masses, hepato- or splenomegaly, and signs of cirrhosis, such as ascites and venous congestion. The examination should also include visual fields, cranial nerves, and fundoscopy for possible pituitary (or other) central nervous system lesions. Look for spider angiomas and palmar erythema (as occur in cirrhosis); warm, moist skin and myxedema

Hereditary hemochromatosis is an important and often overlooked cause of hypogonadism.

A case where drug therapy was to blame

Jed G is a 61-year-old man who reported decreased libido and erectile dysfunction. Examination revealed normal male external genitalia and prostate. Gynecomastia was not present. Laboratory results were: total testosterone, 159 ng/dL (normal, 241-827); free testosterone, 40 pg/mL (47-244); follicle-stimulating hormone (FSH), 9.1 mIU/mL (1.4-18.1); luteinizing hormone (LH), 3.4 mIU/mL (1.5-9.3); prolactin, 2.8 ng/mL (2.1-17.7); and normal values for ferritin and iron. His prostate-specific antigen (PSA) level was 0.8 ng/mL (normal, 0.00-4.00 ng/mL).

Mr. G was started on testosterone 1% gel at 5 g/d. The repeat total testosterone measurement was 215 ng/dL, and free testosterone was 82 pg/mL. The patient discontinued the testosterone gel a few months later due to the medication's high cost.

Several years later, his total testosterone level had fallen to 110 ng/dL, and he continued to complain of fatigue, decreased libido, and erectile dysfunction. We initiated testosterone enanthate 100 mg IM every 3 weeks, which increased his testosterone level to 285 mg/dL. However, hemoglobin increased to 18.3 g/dL, and he noted bilateral nipple tenderness since the start of the injections. Small bilateral gynecomastia about 1 cm in diameter was noted. Testosterone injections were discontinued due to the erythrocytosis. The breast tenderness and gynecomastia resolved 4 months later.

Mr. G had idiopathic hypogonadism. The breast tenderness and gynecomastia he developed were most likely a result of peripheral aromatization of testosterone. This is similar to gynecomastia commonly observed during early puberty and would likely have regressed with continued therapy. However, as noted above, the testosterone injections had to be stopped due to significant erythrocytosis.

Although theoretically promising, results of the few controlled trials with aromatase inhibitors have been generally disappointing.

(as in Graves' disease); and mucocutaneous lentigines (as in Peutz-Jeghers syndrome).[10]

When laboratory and radiologic testing may help

Most adolescents with gynecomastia are best managed by reassurance and observation[11] (**ALGORITHM**),[3] and no laboratory or radiographic studies are recommended in most cases. Exceptions would be gynecomastia that develops before the onset of puberty; evidence of undervirilization on physical examination; a testicular mass; or persistence of gynecomastia beyond the usual observation period of 12 to 18 months.[11]

If findings on physical examination are consistent with a breast neoplasm, arrange for mammography immediately. The sensitivity and specificity of mammography for benign and malignant conditions exceed 90%.[12] A biopsy may be necessary if uncertainty remains after imaging.

No specific tests are necessary when gynecomastia is clearly associated with intake of a medication known to be associated with the condition, especially if the history and examination are otherwise negative. A prompt regression of gynecomastia after discontinuation of the offending drug will confirm the diagnosis.

If the condition persists in an adolescent or adult and the cause is still unclear, perform renal function tests and measure levels of liver enzymes, early-morning serum human chorionic gonadotropin (hCG), LH, total testosterone, estradiol, TSH, and prolactin.

What lab results may mean. If the total testosterone level is borderline or low-normal (200-350 ng/dL), repeat the test and measure the free testosterone level.

If an elevated hCG level is found, repeat the testicular examination carefully and order ultrasonography. In the absence of a testicular tumor, consider an MRI of the brain and computed tomography (CT) of the abdomen and chest to help identify an extragonadal hCG-secreting tumor.

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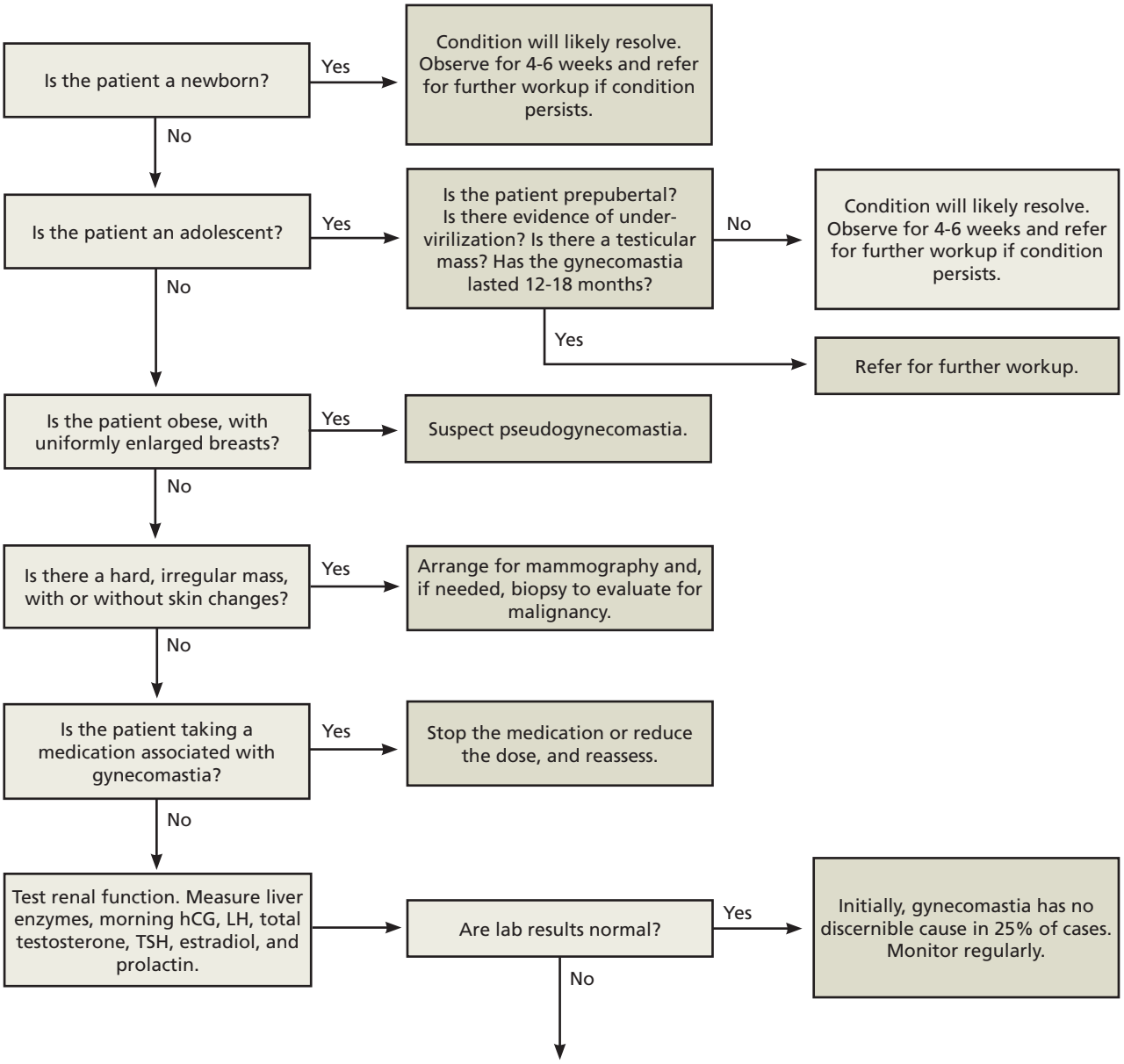
ALGORITHM

Evaluating gynecomastia[3]



↑ hCG or estradiol	↑ LH ↓ testosterone	↑ LH ↑ testosterone	↓↔ LH ↓ testosterone	↓ TSH
Repeat testicular exam and order an ultrasound. If results are negative, order brain MRI and abdominal CT.	Suspect primary hypogonadism. Investigate possible Klinefelter syndrome.	Suspect androgen insensitivity syndrome.	Suspect secondary hypogonadism. If prolactin also ↑, order brain MRI and refer.	Suspect thyrotoxicosis.

CT, computed tomography; hCG, human chorionic gonadotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.

↑ = elevated; ↓ = lowered; ↔ = normal.

Tamoxifen is not yet approved for the treatment of gynecomastia, but it has proven effective in randomized trials.

An elevated LH level and low testosterone level are diagnostic of primary testicular hypogonadism. A karyotype may be necessary in some individuals to diagnose Klinefelter syndrome. Elevated LH and testosterone levels are seen in patients with androgen insensitivity syndromes. These conditions are caused by abnormalities in the androgen receptor with a wide range of possible phenotypes, including ambiguous genitalia.

A low testosterone level with a low or normal LH level indicates secondary hypogonadism of hypothalamic or pituitary origin. An elevated prolactin level in such cases (as was seen in Mr. J.'s case) is usually due to a prolactin secreting pituitary adenoma.

Hereditary hemochromatosis is an important and often overlooked cause of hypogonadism. Obtain iron studies and ferritin levels in this setting.[13] Unrecognized hemochromatosis may result in fibrosis and multiple organ failure.

Patients with secondary hypogonadism are best managed by a referral to an endocrinologist, as the potential list of causes is extensive.[4,14,15]

A low TSH level is consistent with thyrotoxicosis, which may result in increased levels of SHBG and altered metabolism of estrogens and androgens.[16] Thus, about 10% of men with thyrotoxicosis present with gynecomastia and erectile dysfunction.[16] If the estradiol level is elevated, a testicular ultrasound as well as an adrenal CT scan will help identify a neoplasm.

In a significant number of patients, the diagnostic tests are normal, leading to a diagnosis of idiopathic gynecomastia. In these cases, the alteration in androgen and estrogen levels can be subtle and intermittent.[17] Continue surveillance and periodically re-evaluate the patient.

Management of gynecomastia

Gynecomastia often results from transient hormonal imbalance and regresses spontaneously. Therefore, no specific treatment is necessary for neonatal, pubertal, or drug-induced gynecomastia. In other situations, prompt diagnosis and treatment are important to maximize the likelihood of successful medical therapy. It has been shown that fibrosis develops 6 to 12 months after the onset of gynecomastia, making it unlikely that medical treatments beyond that stage will result in significant regression of the breast enlargement.[18] In such long-standing cases, surgical intervention with subcutaneous mastectomy or liposuction can be considered for patients who have significant psychological problems or esthetic issues. Indications for surgery also include continued growth and tenderness of breast tissue or malignancy.

Available medications include those aimed at decreasing estrogen production or estrogen effect on target breast tissue. Aromatase inhibitors such as testolactone, anastrozole, and letrozole can decrease the synthesis of estrogen by inhibiting aromatization of androgens. Although theoretically promising, results of the few controlled trials with aromatase inhibitors have been generally disappointing.[19]

Selective estrogen receptor modulators that alter the effect of estrogen on breast tissue are tamoxifen and raloxifene. Tamoxifen is not yet approved for treatment of gynecomastia, but has proven effective in randomized trials.[20] At a dose of 20 mg/d for 3 or more months, tamoxifen resulted in complete regression of gynecomastia in 60% of patients and partial regression in 20% of patients.[20] Tamoxifen also prevents gynecomastia after medial prostatectomy and treatment with the antiandrogen, bicalutamide.

CASE ▶ Mr. J had a pituitary prolactin-secreting microadenoma causing secondary hypogonadism and gynecomastia. He was started on cabergoline (a dopamine agonist) 0.5 mg orally once a week. Four months later, his total testosterone level was 291 ng/dL, and prolactin was 9.3 ng/mL. His headaches and gynecomastia had significantly decreased. He continued to do well on the same regimen and, 6 years later, his prolactin level was 1.4 ng/mL, indicating that treatment had been effective. **JFP**

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