



# GYNECOMASTIA



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About 30% of males are affected during their life with gynecomastia. Since it causes anxiety, psychosocial discomfort and fear of breast cancer, early diagnostic evaluation is important and patients usually seek medical attention.<sup>1</sup>

True gynecomastia is the glandular enlargement of male breast, which may be unilateral, asymmetrical and tender. It is caused by excess estrogen action. It may be the first pathological expression of estrogen excess or androgen deficiency.

Pseudo gynecomastia occurs in obese men, which is fat deposition instead of glandular hyperplasia.

Physiological gynecomastia can happen in neonatal period, puberty or even in adolescence.

Transient gynecomastia occurs in  $2/3^{\text{rd}}$  of newborns because of maternal estrogen influence and regresses within 3 weeks of birth.

Pubertal gynecomastia usually begins at age 10-12-years-old and peaks at ages 13-14. It usually regresses within 18 months and is uncommon in males aged 17 and older.<sup>2</sup>

Gynecomastia of aging can occur in otherwise healthy elderly males in their 50s to 80s and is secondary to decreased testosterone synthesis or increased body fat which augments aromatization of testosterone to estrogen.

## Common causes of gynecomastia are

### Physiological causes

- Neonatal period, puberty, aging

### Pathological causes

#### 1. Decreased production or action of androgen -

Primary hypogonadism (Klinefelter's syndrome, trauma, viral orchitis, vascular insufficiency, androgen resistance, enzymatic defects in the testosterone biosynthesis pathway).

Secondary hypogonadism

2. **Increased estrogen production** - testicular, adrenal or ectopic tumor/ carcinoma producing estrogen or HCG, true hermaphroditism

3. **Systemic illness** – chronic liver or kidney disease, thyrotoxicosis

4. **Drugs** – estrogens and their analogs, antiandrogens ( finasteride ), growth hormone, gonadotropins, calcium channel blockers, ACE inhibitors, digoxin, cimetidine, ranitidine, methotrexate, phenytoin, isoniazid, ketoconazole, metoclopramide, anabolic steroids, etc.,

5. **Lack of proper nutrition**

## 6. Idiopathic

### Mechanism of action

#### 1. Decreased production and effect of androgens.

The deficiency of testosterone production as in **primary hypogonadism**, leads to a compensatory increase in LH release and enhanced aromatization of testosterone to estradiol, resulting in relative estrogen excess.

2. In secondary hypogonadism, **pituitary gland fails to produce LH, leading to decreased testosterone secretion**, but the adrenal cortex continues to produce estrogen precursors that are aromatized in extraglandular tissues. The net effect is an estrogen – androgen imbalance.<sup>4</sup>

#### 3. Ineffective testosterone action due to defects in or absence of intracellular androgen receptor in androgen target tissues.

In androgen insensitivity syndrome, genotypic male appears as phenotypic female with good breast development.

4. **Increased production of estrogen** - Estrogen acts as a growth hormone of the breast and therefore excess of estradiol in men leads to breast enlargement by inducing ductal epithelial hyperplasia, ductal elongation and branching, the proliferation of periductal fibroblasts and vascularity.<sup>5</sup>

Leydig and Sertoli cell tumors and feminizing adrenocortical carcinomas secrete estrogen. Germ cell tumors of the testis or bronchogenic carcinoma can secrete HCG, which in turn, stimulates Leydig cell aromatase activity and leads to increased conversion of androgen precursors to estrone and estradiol.

5. **Systemic illness** - About 2/3<sup>rd</sup> of patients with liver cirrhosis have gynecomastia. Increased production of androstenedione from adrenals as well as enhanced aromatization to estrone and estradiol are the possible mechanisms. Upto 50% of patients with CKD on hemodialysis may have gynecomastia because of Leydig cell dysfunction, leading to decreased testosterone levels.

6. **Drugs** – Estrogen and analogs and gonadotropins increase estrogenic activity in plasma. Antiandrogens like spironolactone block androgen receptors and alter androgen – estrogen ratio.

### Management

**1. Diagnosis :** History taking must elicit time of onset,, presence of pain, nipple discharge, virilisation symptoms, medication list, systemic illnesses like thyrotoxicosis, kidney or liver disease.

The physical examination should focus on breast and testicular examination, assessment of virilisation and to rule out systemic diseases.

If it is medication related, discontinuation of the offending drugs with resultant improvement confirms the etiology. In peri pubertal boys with no visible cause and normal physical and genital examination, reassessment at the end of six months is appropriate and further tests would be necessary if the symptoms do not recede by then.

In elderly men, it is important to differentiate between gynecomastia from pseudo gynecomastia by breast palpation. True gynecomastia is characterized by feeling of ridges of glandular tissues , fibrous like cord and rubbery to firm in consistency, which are absent in the latter condition.

Periodic follow up is appropriate in asymptomatic patients in whom gynecomastia was discovered during routine examination with no underlying disease and not on any causative drugs.

If gynecomastia is of recent onset, rapid growth, tender or in a lean man, extra investigations are necessary. Biopsy is warranted in the presence of lump.

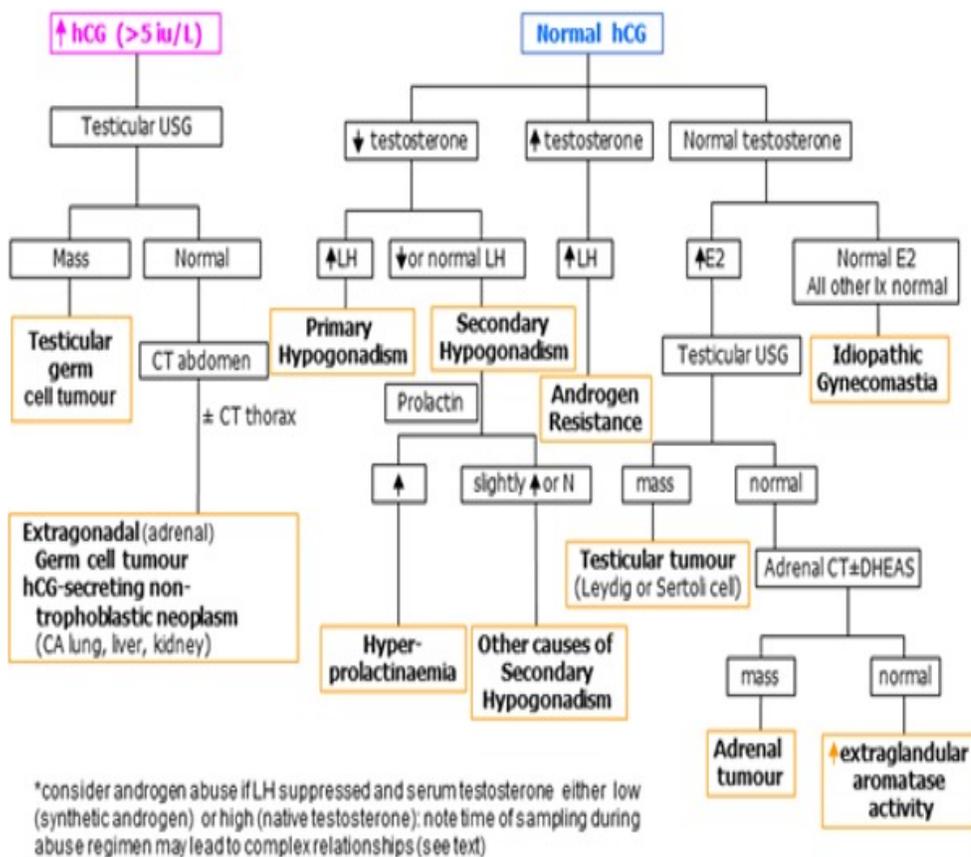
If testes are small, karyotype analysis will rule out Klinefelter's syndrome. A workup of testicular tumor is necessary if they are asymmetrical.

**2. Laboratory Investigations :** testosterone, estradiol, LH and HCG are the important hormonal investigations. Interpretation of these is explained in table below.

- $\uparrow$  LH +  $\downarrow$  testosterone = primary hypogonadism
- $\uparrow$  LH +  $\downarrow$  testosterone + normal PRL = secondary hypogonadism
- $\downarrow$  LH +  $\downarrow$  testosterone +  $\uparrow$  PRL = hyperprolactinemia causing hypogonadism
- $\uparrow$  LH +  $\uparrow$  testosterone = androgen resistance
- $\uparrow$   $\beta$  HCG + testicular mass = testicular germ cell tumor
- $\uparrow$  estradiol + testicular mass = Leydig / Serotoli cell tumor
- $\uparrow$  estradiol + normal testes = rule out adrenal neoplasm
- All the reports normal = Idiopathic gynecomastia

**3. Treatment :** Identify and treat the underlying cause. Table 3 depicts various treatment options depending on the cause.  
 Pubertal gynecomastia = Observation  
 Continued growth, tenderness, cosmesis = Surgery  
 Leydig cell, Sertoli cell or granulosa cell tumors = surgery

Figure 1 below is the flow chart - How to arrive at the diagnosis with the help of laboratory investigations <sup>6</sup>.



3 classes of medical treatment for gynecomastia: androgens (testosterone, dihydrotestosterone, danazol), anti-estrogens (clomiphene citrate, tamoxifen), and aromatase inhibitors such as letrozole and anastrozole.

Moderate pain or increase in size and other causes ruled out = medical management, Tamoxifen 10 mg bd <sup>7</sup>

Surgery should also be deferred until the underlying cause of gynecomastia has resolved or been treated.

Surgical treatment for benign causes includes removal of glandular tissue coupled with liposuction. Minimally invasive surgery is associated with few complications and prompt recovery.

### Key points and summary:

- Gynecomastia is caused by an imbalance between circulating levels of androgens and estrogens.
- Careful drug history should be elicited in all patients of gynecomastia.
- A thorough clinical examination of the breast, testes and examination to rule out systemic disorders is must.
- Key laboratory tests include serum testosterone,  $\beta$  HCG, LH and estradiol.
- Testicular ultrasound, adrenal CT or MRI may be needed to rule out neoplasm.
- Diagnosis of idiopathic gynecomastia should only be made if other causes are ruled out.
- Correction of underlying is the key treatment and that resolve gynecomastia.

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