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REVIEW ARTICLE

# Gynecomastia

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**Abstract**
Enlargement of breasts among boys is termed gynecomastia. This could be due to an alteration in the androgen-estrogen ratio along with the effects of other hormones including growth hormone, insulin like growth factor 1, prolactin, and other factors affecting aromatase enzyme. The common causes of gynecomastia are pubertal gynecomastia, obesity, drugs and hypogonadism. Several other diseases including liver or renal failure, thyrotoxicosis, Klinefelter syndrome, tumors and environmental pollutants can cause gynecomastia. History and clinical examination will help formulate targeted investigations and management. The factors to be evaluated in these include examination of breasts and testes, in addition to other parts of systemic examination. Treatment of underlying disorders can improve gynecomastia, such as use of testosterone in hypogonadism. Some boys may not need any intervention as gynecomastia may resolve on its own. Medical management is useful in simple gynecomastia. Tamoxifen has been tried successfully in adolescents with gynecomastia. Other drugs including clomiphene, danazol, letrozole and anastrozole have not been consistently useful in this age group. In severe chronic gynecomastia, surgery is the treatment of choice.

**Keywords** Gynecomastia · Estrogen · Aromatase · Tamoxifen · Surgery

## Introduction

Gynecomastia is usually a benign generalized glandular enlargement of breast tissue in males. But, the etiology may sometimes be worrisome. Enlargement of breasts could be unilateral or bilateral and the reasons are myriad with the etiology varying with age. In contrast, lipomastia or pseudogynecomastia is noted in obese boys due to accumulation of fat in the region of breast.

## Pathophysiology

The development of breast tissue in the pre-pubertal period is similar in normal boys and girls. Epidermis from the primitive areolar region proliferate into ducts which are connected to the skin surface at the nipple. The inner ends of these ducts bud and form alveoli. Several hormones positively influence this process including prolactin (PRL), placental estrogen and progesterone. Development beyond this stage is quiescent until puberty.

Estrogen, progesterone, prolactin, growth hormone - insulin like growth factor 1 (GH-IGF1) influence the development of breast positively while testosterone impacts this growth negatively [1]. Any imbalance in these hormonal effects can lead to the development of gynecomastia in boys. A complex interaction between estrogen and progesterone with the GH-IGF1 is responsible for the growth of mammary tissue as evident by absence of mammary growth in the absence of GH-IGF1 during animal experiments [2]. Tissues from gynecomastia demonstrate receptors of estrogen, progesterone and androgens. PRL plays a role by stimulating proliferation of the epithelial cells of the breast in the presence of estrogen. It also improves the differentiation of the alveoli and lobules in the presence of progesterone [1].

Histological examination of gynecomastia reveals benign proliferation of breast tissue. Enlargement of breast in males happen due to an imbalance between the action of male sex steroids and estradiol. This can happen in several ways. Estrogens in males could come from a primary source or by aromatization of male sex steroids. Moreover, breast tissue in gynecomastia has demonstrated receptors of estrogen, progesterone and androgen [1].

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During the initial 6 mo of gynecomastia, there is ductal epithelial hyperplasia, increase in connective tissue, increased periductal inflammation and edema with proliferation of fibroblasts. In the later stages (after 12 mo), fibrosis happens with very little proliferation or inflammation or edema. Hence, pain and tenderness are not noticeable in the later stages and therapeutic options would vary between early and late stages [1]. Enlargement of breasts in young boys could be physiological or due to pathological causes (Table 1).

## Physiological Gynecomastia

Gynecomastia can happen physiologically during three stages of a man's life. The breasts maybe transiently enlarged during the neonatal period and early infancy due to the transplacental transfer of maternal hormones and due to the gonadotropin surge of minipuberty of young.

Similarly, gynecomastia might be present in a significant proportion of boys during their normal pubertal development and this is termed pubertal gynecomastia. Androgen to estrogen ratio is low among boys with pubertal gynecomastia and some studies have shown increased aromatase activity in the skin fibroblasts of these boys [7].

The third stage where gynecomastia may be commonly seen is among older men. Reduced testosterone due to aging along with increased aromatase activity due to increased fat maybe responsible for gynecomastia in older men.

## Pathological Gynecomastia

Estrogen excess or reduced testosterone are reasons for gynecomastia. Presenting complaint and clinical features of elevated concentrations of estrogen are dependent on the age of the boy and etiology.

**Table 1** Etiology of gynecomastia in children and adolescents [1, 3–6]

| | |
|---|---|
| Physiological | 1. Transplacental transfer of maternal hormones or increased aromatization of androgens due to neonatal LH surge<br>2. Puberty |
| Pathological | 1. Estrogen excess<br>2. Reduced testosterone<br>Other causes:<br>1. Drugs<br>2. Tumors<br>3. Primary and secondary hypogonadism<br>4. Inherited defects of reduced testosterone biosynthesis or action<br>5. Others – liver disease, chronic kidney disease, HIV, hypothyroidism, hyperthyroidism<br>6. Idiopathic |

A small proportion of peripheral estrogen in the circulation of post-pubertal boys come from the testes. This includes 15% of estradiol & 5% of estrone and the rest comes from aromatization of testosterone and androstenedione.

Other causes of gynecomastia:

- Drugs: They cause gynecomastia through different mechanisms. Some block the production or effects of testosterone, while others may cause testicular damage or stimulate the production of estrogen. Several drugs that could cause gynecomastia are digitalis, growth hormone, ranitidine, spironolactone, ketoconazole, flutamide, metronidazole, proton pump inhibitors, isoniazid [3].
- Tumors: While some tumors produce excess estrogen, others overproduce androgens with peripheral aromatization and cause gynecomastia. Some tumors secrete excess human chorionic gonadotropin (HCG) which can directly stimulate Leydig cells through lutenizing hormone (LH) receptors. These tumors could be benign or malignant and include Leydig & Sertoli cell tumors, granulosa cell tumors, gonadal and extra gonadal germ cell tumors or adrenal masses [1].
- Primary hypogonadism: Testicular failure following viral or bacterial orchitis, torsion, supernumerary X such as Klinefelter syndrome and other similar diseases can cause gynecomastia due to reduction in testosterone and consequent increase in LH which increases aromatization [1, 4].
- Secondary hypogonadism: Reduced testosterone in diseases such as Kallman syndrome (secondary hypogonadism with anosmia), suprasellar & sellar tumors, surgery, and radiation can cause an unopposed action of estrogens that are obtained by the aromatization of the adrenal androgens [4].
- Inherited defects of testosterone biosynthesis and activity such as androgen insensitivity syndrome, Kennedy syndrome could produce a reduced sensitivity of the androgen receptors or reduction in testosterone concentrations.
- General causes: Hyperthyroidism (increases activity of peripheral aromatase and increases LH), liver failure, end stage renal disease, HIV, phytoestrogens (estrogens from plant sources), xenoestrogens (estrogens from chemicals, plastics, preservatives) could lead to gynecomastia [5, 6].

## History and Clinical Examination

A detailed history is essential with special focus on the following points:

Onset and duration of breast enlargement, any change in shape of breasts or presence of discharge from nipples, regional node enlargement, associated illnesses such as mumps with orchitis in the past, prolonged use of any medication, past history of systemic illness or tumors or

undescended testes and any family history of gynecomastia [3]. It is helpful to assess if it is unilateral or bilateral and follow the plan mentioned in Fig. 1.

History and clinical examination focusing on the presence of other diseases such as obesity, thyrotoxicosis, hepatic and renal failure, visual field assessment for evaluation of pituitary disease should be specifically focused upon. Progressive increase in body mass index is associated with increased prevalence of gynecomastia, which is probably due to paracrine effects happening in the fat of the sub-areolar breast tissue [8]. Clinical examination of testes is an essential part of the systemic evaluation of gynecomastia.

Examination of the gynecomastia should be performed in the supine position with his hands clasped behind the head. The thumb and forefinger of the examiner are moved from either side of the breast towards the nipple and areola (Supplementary Fig. S1). A firm concentric disc like breast tissue is felt along with the nipple-areolar complex in gynecomastia. A nodule of more than 2 cm in the sub-areolar region is considered significant [4]. No such separate concentric tissue is felt in pseudogynecomastia. Presence of chronic gynecomastia is less sinister and tenderness is uncommon, if it has been present for more than six months [4]. Complete examination of the breast includes size, tenderness, mobility, tethering, puckering of skin, consistency on palpation and presence of regional nodes.

Gynecomastia in boys has been classified into 4 grades of increasing severity. These range from simple areolar protrusion to female appearance of breasts. Cordova and Morschella had proposed a morphological classification based on the relationship between the nipple and areola with the inframammary fold [9].

Grade 1 - Gynecomastia is limited to the areolar region
Grade 2 - Nipple areolar complex is above the inframammary fold
Grade 3 - Nipple areolar complex is at or 1 cm below the inframammary fold
Grade 4 - Nipple areolar complex is more than 1 cm below the inframammary fold

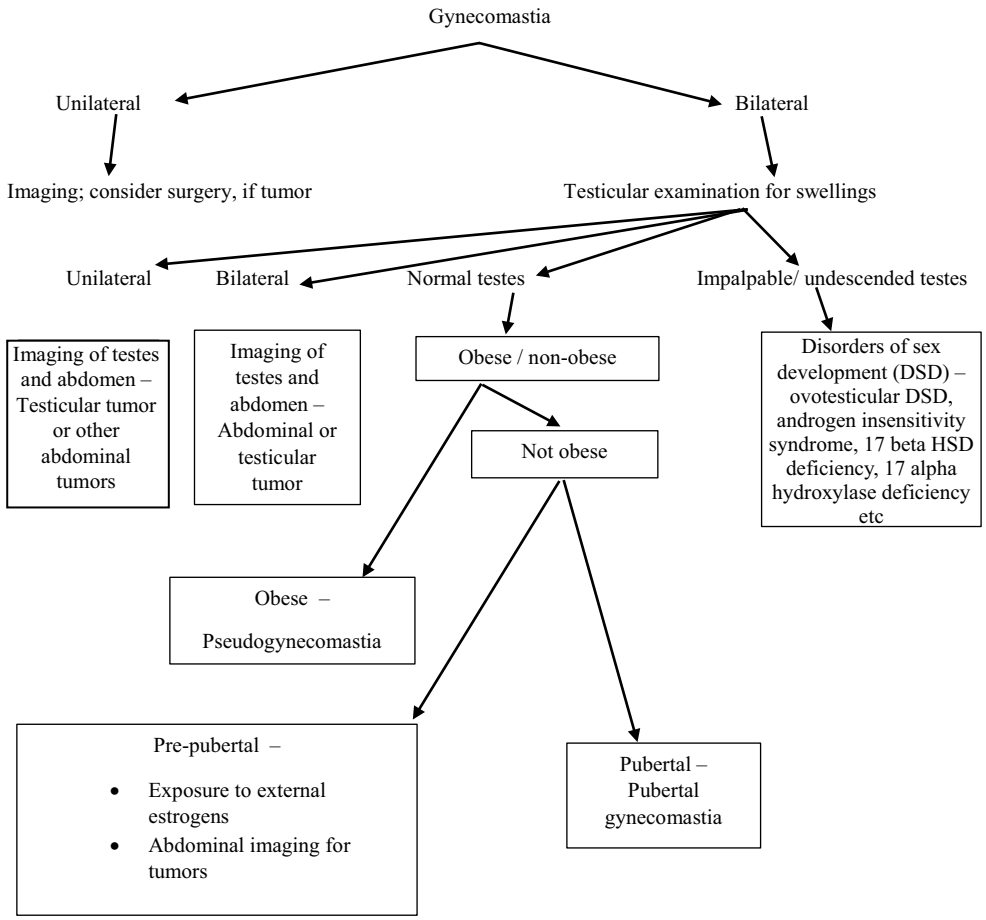


**Fig. 1** Approach to gynecomastia in children and adolescents

**Table 2** Clinical differences between simple gynecomastia and carcinoma of breast [1]

| | Gynecomastia | Carcinoma of the breast |
|---|---|---|
| Consistency | Soft, firm or elastic | Firm to hard |
| Laterality | Usually bilateral | Commonly unilateral |
| Locality | Concentric tissue with the nipple-areolar complex | Located outside the nipple-areolar complex |
| Skin over the swelling | Normal | Dimpling of skin or retraction of nipple may be seen |
| Nipple discharge | Usually absent | Fluid or bloody discharge may be present |

Though carcinoma of the breast is extremely rare in young boys and adolescents, it is important to differentiate this from gynecomastia, as explained in Table 2 [1].

Evaluation of the psychological status of the boy is imperative as the treatment of gynecomastia will focus significantly on the outcomes expected by the boys.

## Targeted Investigations

Laboratory evaluation will be based on the history and clinical examination. If there is any suspicion of a pathological cause of gynecomastia, blood tests could include estradiol, testosterone, LH, follicular stimulating hormone (FSH), and HCG. Testosterone concentrations are lower and estradiol to testosterone ratio is higher in patients with gynecomastia in comparison with boys having pseudogynecomastia [10].

Low testosterone could indicate hypogonadism. If it is associated with elevated FSH, this could point towards primary testicular failure. Elevated testosterone and LH could suggest androgen resistance. Karyotyping is necessary in patients with suspected Klinefelter syndrome. Liver, renal and thyroid function tests may be necessary in some boys with gynecomastia.

Ultrasound examination of the breasts is necessary in patients with irregular swellings. Abdominal ultrasound along with abdominal and central nervous system (CNS) imaging maybe necessary in some patients.

## Management

Pubertal gynecomastia spontaneously resolves in 85–90% of patients in 6 mo to 2 y [11]. This has to be explained to the boy and his parents when they have lower grades of gynecomastia. Treatment will be needed only for some patients and this will depend on the underlying cause and grade of gynecomastia. Patients with thyrotoxicosis, liver and renal failure are treated for the underlying disease and the regression of gynecomastia depends on the resolution of the underlying disease. Surgical removal of tumors with or without chemotherapy will be attempted based on the type of tumor that resulted in enlargement of breasts [1, 5, 11].

If significant gynecomastia is present in a boy after ruling out any underlying disease, medical management is tried first followed by surgical intervention, if there is failure of medical management. The classes of drugs useful in the management of gynecomastia are mentioned in Table 3, and the choice of medication depends on clinical condition. Treatment started prior to completion of one year from onset produces better results. Initiation of treatment after a year yields poorer results due to underlying fibrosis [4].

Testosterone is useful in patients with hypogonadism. The dose depends on the age and the results that are expected for other aspects of wellbeing, including pubertal onset, progression and the underlying cause of hypogonadism.

In patients with idiopathic gynecomastia, tamoxifen in the dose of 10 mg to 20 mg twice daily has to be used for 3 to 6 mo to assess clinical improvement. Tamoxifen binds to the estrogen receptor and inhibits estrogen effects by binding to the DNA and reduces its effects. This has been noted to be effective in 80% of patients with complete resolution in 60%. In a study evaluating patients treated with tamoxifen, gastritis was noted in 2 patients [12]. Danazol is used in adults, without much use in children. Selective estrogen receptor modulator, raloxifene has been tried in some patients [13]. Letrozole, anastrozole and clomiphene have been tried in a few patients. While anastrazole has not been noted to be useful in adults in comparison to placebo, tamoxifen scored well in management of gynecomastia [1, 5, 13, 14]. A watch on bone mineral density is necessary for patients on this therapy.

Surgical treatment: In patients where medical therapy has failed or when activities of daily living are affected, surgical treatment is attempted. In pubertal gynecomastia, surgery is deferred until the completion of puberty to avoid recurrence. Minimally invasive surgery gives faster recovery to the patient with lesser pain and less scarring. Subcutaneous mastectomy, ultrasound assisted liposuction and suction

**Table 3** Drugs used in management of uncomplicated gynecomastia [1, 3]

| Class of medications | Drugs |
|---|---|
| Androgens | Testosterone, dihydrotestosterone, danazol |
| Anti-estrogens | Tamoxifen, clomiphene, raloxifene |
| Aromatase inhibitors | Letrozole, anastrozole |

assisted lipectomy are some of the procedures that have been tried. Complications that could be associated with surgery are irregular contour, breast asymmetry, hematoma, hypertrophic scars and numbness of the nipple and areolar region [1, 5].

Thus, the therapy has to be individualized for each patient to get the best outcome. In some of these patients including those with pubertal gynecomastia, obesity driven breast enlargement and drug induced gynecomastia can recover without surgery or medications.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s12098-023-04810-7.

## Declarations

**Conflict of Interest** None.

**Guarantor** AA will act as the guarantor for this manuscript.

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