

GYNECOMASTIA: ETIOLOGY, DIAGNOSIS, AND TREATMENT

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ABSTRACT

Gynecomastia is a relatively common disorder. Its causes range from benign physiological processes to rare neoplasms. To diagnose the etiology of the gynecomastia, the clinician must understand the hormonal factors involved in breast development. Parallel to female breast development, estrogen, growth hormone (GH), and IGF-1 are required for breast growth in males. Since a balance exists between estrogen and androgens in males, any disease state or medication that increases circulating estrogens or decreases circulating androgens, causing an elevation in the estrogen to androgen ratio, can induce gynecomastia. Due to the diversity of possible etiologies, including a neoplasm, performing a careful history and physical is imperative. Once gynecomastia has been diagnosed, treatment of the underlying cause is warranted. If no underlying cause is discovered, then close observation is appropriate. If the gynecomastia is severe and of recent onset, medical therapy can be attempted, and if ineffective, glandular tissue can be removed surgically.

INTRODUCTION

This chapter reviews the ontogeny and physiology of breast development; factors that influence breast enlargement in the male; the differential diagnosis of

gynecomastia; the process of diagnostic investigation; and treatment of gynecomastia.

BREAST ONTOGENY AND DEVELOPMENT

Male breast development occurs in an analogous fashion to female breast development. At puberty in the female, a complex hormonal interplay occurs resulting in growth and maturation of the adult female breast.

In early fetal life, epithelial cells, derived from the epidermis of the area programmed to become the areola, proliferate into ducts, which connect to the nipple at the skin's surface. The blind ends of these ducts bud to form alveolar structures in later gestation. With the decline in fetal prolactin and placental estrogen and progesterone at birth, the infantile breast regresses until puberty (1).

During thelarche in females, the initial clinical appearance of the breast bud and growth and division of the ducts occur, giving rise to club-shaped terminal end buds, which then form alveolar buds. Approximately a dozen alveolar buds will cluster around a terminal duct, forming the type 1 lobule. The type 1 lobule will mature into types 2 and 3 lobules, called ductules. The number of alveolar buds

increases to as many as 50 in type 2 and 80 in type 3 lobules. The entire differentiation process takes years after the onset of puberty and, if pregnancy is not achieved, may never be completed (2). On the contrary, there is usually no further development of breast because of the rising testosterone concentrations at puberty. Some peri-pubertal boys may transiently develop type 1 lobules that may undergo atrophy at a later stage.

HORMONAL REGULATION OF BREAST DEVELOPMENT

The initiation and progression of breast development involves a coordinated effort of pituitary and ovarian hormones, as well as local mediators (Figure 1).

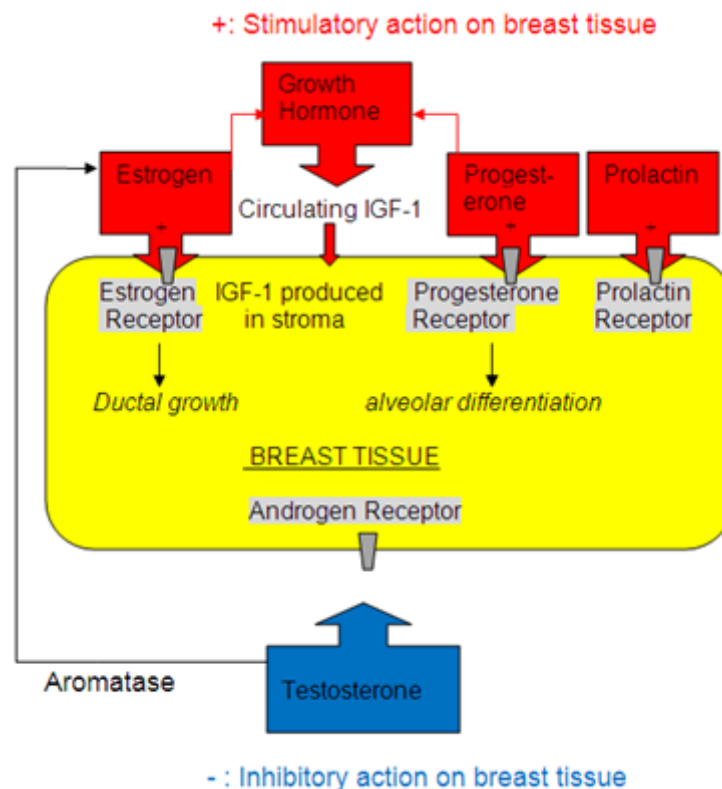


Figure 1. Hormones affecting growth and differentiation of breast tissue.

ESTROGEN, GH AND IGF-1, PROGESTERONE, & PROLACTIN

Estrogen and progesterone act in an integrative fashion to stimulate normal adult female breast development. Estrogen, acting through its estrogen receptor (ER), promotes ductal growth, while

progesterone, acting through its receptor (PR), promotes alveolar development (1). This is demonstrated by experiments in ER knockout mice that display grossly impaired ductal development, whereas PR knockout mice possess significant ductal development, but lack alveolar differentiation (3, 4).

Although estrogens and progestogens are vital to mammary growth, they are ineffective in the absence of anterior pituitary hormones (5). Thus, neither estrogen alone nor estrogen plus progesterone can sustain breast development without other mediators, such as GH and IGF-1. This was confirmed by studies involving the administration of estrogen and GH to hypophysectomized and oophorectomized female rats that resulted in breast ductal development. The GH effects on ductal growth are mediated through stimulation of IGF-1. This is demonstrated by studies of estrogen and GH administration to IGF-1 knockout rats that showed significantly decreased mammary development when compared to age-matched IGF-1-intact controls. Combined estrogen and IGF-1 treatment in these IGF-1 knockout rats restored mammary growth (6, 7). In addition, Walden et al. demonstrated that GH-stimulated production of IGF-1 mRNA in the mammary gland itself, suggesting that IGF-1 production in the stromal compartment of the mammary gland acts locally to promote breast development (8). Furthermore, other data indicates that estrogen promotes GH secretion and increases GH levels, stimulating the production of IGF-1, which synergizes with estrogen to induce ductal development. In a population-based study of healthy boys and adolescents, IGF-I levels were found to be elevated in boys with pubertal gynecomastia compared with boys without gynecomastia suggesting that the GH-IGF-I axis may be involved in the pathogenesis of pubertal gynecomastia (9). Indeed, dating back to 1950, it had already been reported that gynecomastia was found in a young patient with acromegaly (97).

Progesterone has minimal effects on breast development without concomitant anterior pituitary hormones, indicating that progesterone also interacts closely with pituitary hormones. For example, prolonged treatment of dogs with progestogens such as depot medroxyprogesterone acetate or with

proligestone was associated with increased GH and IGF-1 levels, suggesting that progesterone may stimulate GH secretion (10). In addition, clinical studies have correlated maximal cell proliferation to specific phases in the female menstrual cycle. For example, maximal proliferation occurs not during the follicular phase when estrogens reach peak levels and progesterone is low (less than 1 ng/mL [3.1 nmol/mL]), but rather, it occurs during the luteal phase when progesterone reaches concentrations of 10-20 ng/mL (31- 62 nmol/mL) and estrogen concentrations are two to three times lower than in the follicular phase (11). Furthermore, immunohistochemical studies of ER and PR showed that the highest percentage of proliferating cells, found almost exclusively in the type 1 lobules, contained the highest percentage of ER and PR positive cells (2). Similarly, there is immunocytological presence of ER, PR, and androgen receptors (AR) in gynecomastia and male breast carcinoma. ER, PR and AR expression was observed in 100% (30/30) of gynecomastia cases (12). Given these data and the fact that PR knockout mice lack alveolar development in breast tissue, it seems that progesterone, analogous to estrogen, increases GH secretion and acts through the PR on mammary cells to enhance breast development and alveolar differentiation (13, 4).

Prolactin is another anterior pituitary hormone integral to breast development. Prolactin is not only secreted by the pituitary gland but may be produced by normal mammary tissue epithelial cells and breast tumors (14, 15). Prolactin stimulates epithelial cell proliferation only in the presence of estrogen and enhances lobulo-alveolar differentiation only with concomitant progesterone. Gynecomastia is seen rarely in hyperprolactinemia, possibly because of the low estrogen levels due to suppression of LH secretion. Previously, receptors for LH/ human chorionic gonadotropin (hCG) have been found in male and

female breast tissues, but their functional roles remain to be determined (16).

ANDROGEN AND AROMATASE

Estrogen effects on the breast is the result of circulating estradiol levels or locally produced estrogens. Aromatase P450 catalyzes the conversion of the C19 steroids-- androstenedione, testosterone, and 16- α - hydroxyandrostenedione-- to estrone, estradiol-17 β and estriol. As such, an overabundance of substrate (e.g., testosterone) or an increased enzyme activity (aromatase) for estrogen production can increase serum and breast estrogen concentrations and initiate the cascade to breast development in females and males. For example, in the more complete forms of androgen insensitivity syndromes in genetically male (XY) patients, excess androgen is aromatized into estrogen that results in gynecomastia and an overall phenotypic female appearance. Furthermore, the loss of the anti-proliferative effect of androgens on breast also contributes significantly to breast development in XY individuals with complete androgen insensitivity. Likewise, the biologic effects of over-expression of the aromatase enzyme in female and male mice transgenic for the aromatase gene result in increased breast proliferation. In female transgenics, over-expression of aromatase promotes the induction of hyperplastic and dysplastic changes in breast tissue. Over-expression of aromatase in male transgenics causes increased mammary growth and histological changes similar to gynecomastia, increased estrogen and progesterone receptors, and increased downstream breast growth factors such as TGF- β and β FGF (17). Interestingly, treatment with an aromatase inhibitor leads to involution of the mammalian gland phenotype (18). Thus, although androgens do not stimulate breast development directly, they may do so if they aromatize to estrogen.

This occurs in cases of androgen excess or in patients with increased aromatase activity.

PHYSIOLOGIC GYNECOMASTIA

Gynecomastia, breast development in males, can occur normally during three phases of life. The first occurs shortly after birth in both males and females. This is partly caused by the high fetal blood levels of estradiol and progesterone (produced by the mother) that stimulate breast tissue in the newborn. Another mechanism is the increased conversion of steroid hormone precursors to sex steroids and increased aromatization of androgen as a result of neonatal surge of luteinizing hormone (LH). Neonatal gynecomastia may persist for several weeks after birth and may be associated with a milky breast discharge called "witch's milk" (2).

Puberty marks the second period when gynecomastia can occur physiologically. In fact, up to 60% of boys have clinically detectable gynecomastia by age 14. Although it is mostly bilateral, it is often asymmetrical and can occur unilaterally. Pubertal gynecomastia usually resolves within 3 years of onset (2). In early puberty, the pituitary gland releases gonadotropins at night and stimulates testicular production of testosterone during the very early morning hours. Serum estradiol concentration, however, remains elevated above prepubertal concentrations throughout the day. Compared with boys who do not develop gynecomastia, boys with pubertal gynecomastia have a decreased androgen to estrogen ratio (19, 100). Furthermore, another study showed increased aromatase activity in the skin fibroblasts of boys with gynecomastia (103). Thus, the mechanism by which pubertal gynecomastia occurs may be due to either decreased production of androgens or increased aromatization of circulating androgens, thus increasing the estrogen to androgen ratio (20).

The third age range in which gynecomastia is frequently seen is during older age (>60 years). The reported prevalence varies from 36 to 57%, possibly because of different selected populations and different diagnostic criteria (101). Although the exact mechanisms by which this occurs have not been fully elucidated, evidence suggests that it may result from increased peripheral aromatase activity secondary to increased total body fat, relatively elevated LH concentrations, and decreased serum testosterone concentrations associated with male aging. For instance, investigators have shown increased urinary estrogen concentrations in obese individuals and have demonstrated aromatase expression in adipose tissue (21). Thus, like the gynecomastia of obesity, the gynecomastia of aging may partly result from increased aromatase activity, causing increased conversion of androgens to estrogens (22). Moreover, not only does total body fat increase with age, but there may be an increase in aromatase activity in the adipose tissue already present, further increasing circulating estrogens. Serum sex hormone binding globulin (SHBG) concentrations increase with age in men. Because SHBG binds estrogen with less affinity than testosterone, the bioavailable estradiol to bioavailable testosterone ratio may increase in older men. Lastly, elderly patients may take multiple medications associated with gynecomastia. One cohort study suggests medications play a role in 80% of gynecomastia in older men (23).

PATHOLOGIC GYNECOMASTIA

Pathologic gynecomastia is due to an increase in the circulating and/or local breast tissue ratio of estrogen to androgen.

Increased Estrogen

Breast development requires the presence of estrogen. Androgens, on the other hand, have anti-proliferative effects on breast tissue. Thus, an equilibrium exists between estrogen and androgens in the adult male to prevent growth of breast tissue, whereby either an increase in estrogen or a decrease in androgen can tip the balance toward gynecomastia. Increased estrogen levels will increase glandular proliferation by several mechanisms. These include direct stimulation of glandular tissue and by suppressing LH, therefore decreasing testosterone secretion by the testes and exaggerating the already high estrogen to androgen ratio. Since the development of breast tissue in males occurs in an analogous manner to that in females, the same hormones that affect female breast tissue can cause gynecomastia. In post-pubertal boys and adult men, the testes secrete 6-10 µg of estradiol and 2.5 µg of estrone per day. Testicular production comprises a small fraction of estrogens in circulation (i.e., 15% of estradiol and 5% of estrone), and the remainder of estrogen in men is derived from the extraglandular aromatization of testosterone and androstenedione to estradiol and estrone (24). Thus, any cause of estrogen excess from overproduction to peripheral aromatization of androgens can initiate the cascade to breast development.

TUMORS

Testicular tumors can lead to increased blood estrogen levels by the following mechanisms: estrogen overproduction, androgen overproduction with extragonadal aromatization to estrogens, and secretion of hCG that stimulates normal Leydig cells (via the LH receptor). Tumors causing an overproduction of estrogen represent an unusual but important cause of estrogen excess. Examples of estrogen-secreting tumors include Leydig cell tumors, Sertoli cell tumors, granulosa cell tumors, and adrenal tumors.

Leydig cell tumors constitute 1%-3% of all testicular tumors. Usually, they occur in men between the ages of 20 and 60, although up to 25% of them occur prepubertally. In prepubertal cases, isosexual precocity, rapid somatic growth, and increased bone age with elevated serum testosterone and urinary 17-ketosteroid levels are the presenting features. In adults, elevated estrogen levels coupled with a palpable testicular mass and gynecomastia suggests a testicular tumor. Of note, feminization (particularly gynecomastia) is common in adults, but it is rare in boys. Some Leydig cell tumors may only be apparent on ultrasound because of their small size; some may produce testosterone and do not cause gynecomastia. Though mostly benign, Leydig cell tumors may be malignant and metastasize to lung, liver, and retroperitoneal lymph nodes (25, 26).

Sertoli cell tumors comprise less than 1% of all testicular tumors and occur at all ages, but one third have occurred in patients less than 13 years, usually in boys under 6 months of age. Although they arise in young boys, they usually do not produce endocrine effects in children. Again, the majority are benign, but up to 10% are malignant. Gynecomastia occurs in one third of cases of Sertoli cell tumors, presumably due to increased estrogen production (26). Sertoli cell tumors in boys with Peutz-Jegher syndrome, an autosomal dominant disease characterized by pigmented macules on the lips, gastrointestinal polyposis, and hormonally active tumors in males and females, for instance, have aromatase overactivity, resulting in gynecomastia, rapid growth, and advanced bone age as presenting features (29, 30, 31). Feminizing Sertoli cell tumors with increased aromatase activity can also be seen in the Carney complex, an autosomal dominant disease characterized by cardiac myxomas, cutaneous pigmentation, adrenal nodules and hypercortisolism

Granulosa cell tumors, occurring very rarely in the testes, can also overproduce estrogen. Gynecomastia at presentation was reported in some cases (27).

Germ cell tumors are the most common cancer in males between the ages of 15 and 35. They are divided into seminomatous and non-seminomatous subtypes and include embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, and teratoma. Elevated serum hCG or hCG subunits (e.g., may be present in both seminomatous and non-seminomatous types of germ cell tumors), whereas AFP may be elevated only in the non-seminomatous type. As a result of the increased hCG that stimulates the Leydig cell via the LH receptor, testicular testosterone and estrogen (estrogen out of proportion to testosterone) production is increased and may cause gynecomastia. Although germ cell tumors generally arise in the testes, they can also originate extragonadally, specifically in the mediastinum. These extragonadal tumors also possess the capability of producing hCG, but they must be differentiated from a multitude of other tumors such as large cell carcinomas of the lung that can synthesize hCG or hCG subunits (28).

Some neoplasms that overproduce estrogens also possess aromatase overactivity. Other than sex-cord tumors, fibrolamellar hepatocellular carcinoma has also been shown to possess ectopic aromatase activity, causing severe gynecomastia in two boys (32, 33).

Furthermore, adrenal tumors can secrete excess dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEAS), and androstenedione that can then be aromatized peripherally to estradiol. Some adrenal tumors may secrete estrogen directly. Typically, feminizing-adrenal tumors are large, aggressive, and malignant (90).

Table 1. Tumors Causing Gynecomastia

Tumor type	Hormone produced	Aromatase overactivity
Leydig cell tumor	Testosterone, estrogen	
Sertoli cell tumor	Estrogen	+ (in Peutz-Jegher syndrome), + (in Carney complex)
Granulosa cell tumor	Estrogen	
Adrenal tumor	Estrogen, dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEA-S), and androstenedione that are converted in the periphery to estrogens.	
Gonadal germ cell tumor	hCG and β -hCG	
Extragenital germ cell tumor e. G lung, gastric, renal cell and hepatocellular carcinoma	hCG and β -hCG	

NON-TUMOR CAUSES OF ESTROGEN EXCESS

Increased Aromatase Activity

Besides tumors, other conditions have also been associated with excessive aromatization of testosterone and other androgens to estrogen leading to gynecomastia. For instance, obesity is strongly associated with gynecomastia. The mechanism is thought to be related to the increased aromatase activity in adipose tissues, but most obese men do not have high estrogen concentrations (104). Leptin has also been implicated in the pathogenesis of gynecomastia because it might stimulate aromatase in adipose and breast tissue. Leptin might also directly

stimulate the growth of epithelial cells in the breast or enhance the sensitivity of epithelial cells to estrogen (98). There is a very rare familial form of gynecomastia in which affected family members have an elevation of extragenital aromatase activity (34). Novel gain-of-function mutations in chromosome 15 have been reported to cause gynecomastia, possibly by forming cryptic promoters that lead to over expression of aromatase (35). Polymorphism of the aromatase cytochrome P45019 (CYP19) has also been found to be associated with gynecomastia (36).

Displacement of Estrogens From SHBG

Another cause of gynecomastia from estrogen excess includes steroid displacement from SHBG. SHBG binds androgens more avidly than estrogen. Thus, any condition or drug such as spironolactone that displaces steroids from SHBG more easily displace estrogen than testosterone, resulting in a higher estrogen to testosterone ratio. Drugs can cause gynecomastia by numerous mechanisms besides displacement from SHBG. These drugs and their mechanisms are discussed below.

Decreased Testosterone and Androgen Resistance

Besides increased estrogen production, decreased testosterone levels can cause an elevation in the estrogen to androgen ratio, thereby producing gynecomastia. Primary hypogonadism, with its reduction in serum testosterone and increased serum LH levels increases aromatization of testosterone to estradiol and is associated with an increased estrogen to androgen ratio. Klinefelter syndrome occurs in 1 in 600-700 males and is caused by supernumerary X chromosomes (XXY or XXXY karyotype) and primary testicular failure and often prominent gynecomastia, due to decreased testosterone production, compensatory increased LH secretion, overstimulation of the Leydig cells, and relative estrogen excess. In addition, any acquired testicular disease resulting in primary hypogonadism such as severe, postpubertal viral and bacterial orchitis, or scrotal trauma or radiation can promote gynecomastia by the same mechanisms (24). Lastly, enzyme deficiencies in the testosterone synthesis pathway from cholesterol also result in depressed testosterone levels and hence a relative increase in estrogen. Deficiency of 17-oxosteroid reductase, the enzyme that catalyzes the conversion of androstenedione to testosterone and estrone and estrone to estradiol, for

example, will cause elevation in estrone and androstenedione, which is then further aromatized to estradiol (22).

Secondary hypogonadism results in low serum testosterone and unopposed estrogen effect from increased conversion of adrenal precursors to estrogens (24). Thus, patients with Kallmann syndrome, a form of congenital secondary hypogonadism with anosmia, also develop gynecomastia. In fact, androgen deficiency (hypogonadism) from whatever cause constitutes most cases of gynecomastia.

The androgen resistance syndromes, including complete and partial testicular feminization are characterized by gynecomastia and varying degrees of pseudohermaphroditism. Kennedy disease, a neurodegenerative disease, is caused by an increased number of CAG (polyglutamine) repeats in the androgen receptor gene that leads to a decrease in sensitivity of the receptor (2). The gynecomastia is the combined result of decreased androgen responsiveness at the breast level and increased estrogen production as a result of elevated androgen precursors of estradiol and estrone. Androgen resistance at the pituitary results in elevated serum LH levels and increased circulating testosterone. The increased serum testosterone is then aromatized peripherally, promoting gynecomastia.

Other Diseases

Men with end-stage renal disease may have reduced testosterone and elevated gonadotropins. This apparent primary testicular failure may then lead to increased breast development (13). The gynecomastia of liver disease, particularly cirrhosis, does not have a clear etiology. Cirrhosis is associated with increased SHBG that binds testosterone more

avidly than estrogen. Some have speculated that the gynecomastia is the result of estrogen overproduction, possibly secondary to increased extraglandular aromatization of androstenedione, which may have decreased hepatic clearance in cirrhosis. However, testosterone administration to patient with cirrhosis causes a rise in estradiol, but decreases the prevalence of gynecomastia (5, 37, 38). Therefore, although the association of gynecomastia with liver disease is apparent, current data are conflicting and the mechanism remains unclear.

Thyrotoxicosis is associated with gynecomastia. Patients often have elevated estrogen that may result from a stimulatory effect of thyroid hormone on peripheral aromatase. In addition, LH is also increased in many men with thyrotoxicosis, and LH also stimulates aromatization of testosterone (13,39, 96). Furthermore, thyroxine stimulates production of SHBG in the liver. Because SHBG binds testosterone more avidly than estradiol, there is a higher ratio of free estradiol to free testosterone. Thus, with normal testosterone and increased estrogen, there is an elevated free estrogen to testosterone ratio.

Gynecomastia is associated with spinal cord disorders. Most patients with spinal cord disorders often have low testosterone levels and, in fact, can develop testicular atrophy with resultant hypogonadism and infertility, which may be exacerbated by increased scrotal temperature. The exact mechanism, however, remains elusive (40).

Refeeding gynecomastia refers to breast development in men recovering from a malnourished state (1). Although most cases regress within several months, the etiology of this phenomenon has not been fully elucidated.

HIV patients can also develop gynecomastia. There is a high incidence of androgen deficiency due to multifactorial causes, including primary and secondary hypogonadism and certain drugs used to treat HIV (e.g., efavirenz) (24).

Drugs

About 20% of gynecomastia is caused by medications or exogenous chemicals (41). Some drugs may increase estrogen effect by several mechanisms: 1) they possess intrinsic estrogen-like properties, 2) they increase endogenous estrogen production, or 3) they supply an excess of an estrogen precursor (e.g., testosterone or androstenedione) that can be aromatized to estrogen. Examples of drugs that cause gynecomastia are listed in Tables 2 and 3. Contact with estrogen vaginal creams, for instance, can elevate circulating estrogen levels. Since some of the creams contain synthetic estrogens, they might not be detected by standard estrogenic qualitative assays. An estrogen-containing embalming cream has been reported to cause gynecomastia in morticians (42, 43). A topical estrogen spray, used for relief of menopausal hot flashes may lead to gynecomastia in children through skin contact (44). Recreational use of marijuana, heroin, methadone, and amphetamines has also been associated with gynecomastia (45). Herbs containing phytoestrogen or ginseng with estrogen-like structure (46) may also lead to gynecomastia. It has been suggested that digitalis causes gynecomastia due to its ability to bind to estrogen receptors (13, 47). The appearance of gynecomastia has been described in body builders and athletes after the administration of aromatizable androgens. The gynecomastia was presumably caused by an excess of circulating estrogens due to the conversion of androgens to estrogen by peripheral aromatase enzymes (48).

Table 2. Drugs That May Induce Gynecomastia by Known or Proposed Mechanisms						
Estrogen-like, or binds to estrogen receptor	Stimulate estrogen synthesis	Supply aromatizable estrogen precursors	Direct Testicular Damage	Block testosterone synthesis	Block androgen action	Displace estrogen from SHBG
Estrogen vaginal cream	Gonadotropins	Exogenous androgen	Busulfan	Ketoconazole	Flutamide	Spironolactone
Estrogen-containing embalming cream	Growth Hormone	Androgen precursors (i.e., androstenedione and DHEA)	Nitrosurea	Spironolactone	Bicalutamide	Ethanol
Delousing powder			Vincristine	Metronidazole	Finasteride	
Digitalis			Ethanol	Etomidate	Cyproterone	
Clomiphene			Tyrosine kinase inhibitor		Zanoterone	
Marijuana*					Cimetidine	
					Ranitidine*	
					Spironolactone	

* Weak evidence

Table 3. Drugs That May Cause Gynecomastia by Uncertain Mechanisms
Cardiac and antihypertensive medications: Calcium channel blockers (verapamil, nifedipine, diltiazem) Angiotensin-converting enzyme Inhibitors* (captopril, enalapril) Alpha-blockers* Amiodarone Methyldopa Reserpine Nitrates
Psychoactive drugs: Neuroleptics Anxiolytic agents* (e.g., diazepam) Phenytoin Tricyclic antidepressants

Haloperidol Atypical antipsychotic agents
Drugs for infectious diseases: Antiretroviral therapy for HIV/AIDS (e.g., efavirenz) Isoniazid Ethionamide Griseofulvin Minocycline
Drugs of Abuse: Amphetamines Heroin Methadone
Others: Theophylline Omeprazole Auranofin Diethylpropion Domperidone Penicillamine Sulindac Heparin Methotrexate Dipeptidyl peptidase 4 inhibitors Statin*

*** Weak evidence**

Drugs and chemicals that cause decreased testosterone levels either by causing direct testicular damage, by blocking testosterone synthesis, or by blocking androgen action can also produce gynecomastia. For instance, phenothrin, a chemical component in delousing agents, possessing anti-androgenic activity, has been attributed as the cause of an epidemic of gynecomastia among Haitian refugees in US detention centers in 1981 and 1982 (49). Chemotherapeutic drugs, such as alkylating agents and tyrosine kinase inhibitors (102), can cause Leydig cell and germ cell damage, resulting in primary hypogonadism. Flutamide, an anti-androgen used as treatment for prostate cancer, blocks androgen action in peripheral tissues. Ketoconazole, on the other hand,

can inhibit steroidogenic enzymes required for testosterone synthesis. 5 α -reductase inhibitors, finasteride and dutasteride, that reduce the conversion of testosterone to dihydrotestosterone may cause gynecomastia (50). They also cause an increase in the synthesis of testosterone and, subsequently estrogen through aromatization. Spironolactone causes gynecomastia (up to 10%) by several mechanisms. Like ketoconazole, it can block androgen production by inhibiting enzymes in the testosterone synthetic pathway (i.e., 17 α -hydroxylase and 17-20-desmolase), but it can also block receptor-binding of testosterone and dihydrotestosterone (51). In addition to decreasing testosterone levels and biologic effects, spironolactone also displaces estradiol from SHBG,

increasing free estrogen levels. Of note, the anti-androgenic property of spironolactone has been used in gender identity disorder (from male to female) and spironolactone is considered to be a cost-saving medication (52). On the other hand, eplerenone is more specific for the mineralocorticoid receptor and less associated with anti-androgenic effects such as gynecomastia (up to 0.5%) (53). Switching from spironolactone to eplerenone may reverse painful gynecomastia induced by spironolactone in patients with cirrhosis (54). Ethanol increases the estrogen to androgen ratio and induces gynecomastia by multiple mechanisms as well. Firstly, it is associated with increased SHBG, which decreases free testosterone levels. Secondly, it increases hepatic clearance of testosterone, and thirdly, it has a direct toxic effect on the testes (24). Besides the drugs stated, a multitude of others have been associated with gynecomastia by unknown mechanisms (92) (Table 3). For many of these drugs, the causal relationship with gynecomastia has not been established or the evidence is weak.

MALE BREAST CANCER

Male breast cancer is rare and comprises only 0.2% of all male cancers. The overall prevalence of invasive carcinomas was 0.11% and of *in situ* carcinomas was 0.18% in a 20-year national registry study of surgically excised breast specimens with the diagnosis of gynecomastia (55). Although male breast cancer is rare and gynecomastia is not considered a premalignant condition (101), men with gynecomastia, especially elderly, worry about breast cancer and often seek medical advice (56) and it is important to differentiate male breast cancer from gynecomastia (Table 4). Of note, men with Klinefelter syndrome have a 20- to 50-fold increased risk of breast cancer. Other risk factors include hyperestrogenic conditions like obesity, alcohol, exogenous estrogen exposure (e.g., gender reassignment), and testicular disorders. It is unclear if these are specific risks for breast cancer are linked to the stimulatory process responsible for gynecomastia (57). Old age, working in environment with high temperature, exhaust emissions, radiation to chest, and liver damage are also risk factors for male breast cancer (58). Family history should always be explored. In particular, a family history of BRCA2 positive breast cancer significantly increases the risk of male breast cancer in carriers of mutation (59).

Table 4. Clinical Findings of Gynecomastia and Male Breast Cancer		
Clinical findings	Gynecomastia	Male breast cancer
Unilateral/ bilateral	Mostly bilateral, can be unilateral	Unilateral
Consistency	Rubbery or firm	Firm or hard
Location	Concentric, around the nipple	More peripheral, outside the nipple
Pain	Painful if recent onset or rapid enlargement	Usually painless
Associated features such as skin dimpling, nipple retraction, bloody discharge	No	Possible
Palpable axillary or supraclavicular lymph node(s)	No	Possible

PATIENT EVALUATION

History Taking and Physical Examination

At presentation, all patients require a thorough history and physical exam. Particular attention should be given to medications, drugs and alcohol abuse, as well as other chemical exposures. Symptoms of underlying systemic illness, such as hyperthyroidism, liver disease, or renal failure should be sought. Furthermore, the clinician must recall neoplasm as a possible etiology and should establish the duration and timing of breast development. Chronic gynecomastia is more reassuring because it is almost never due to malignancy. Additionally, the clinician should inquire about fertility, erectile dysfunction, and libido to rule out hypogonadism.

In our experience, the breast examination is best performed with the patient supine and with the examiner palpating from the periphery to the areola. When firmness is noted, the glandular mass should be measured in diameter. Clinically, gynecomastia is

diagnosed by finding subareolar breast tissue of 2 cm in diameter or greater. Malignancy should be suspected if an immobile, firm mass is found on physical examination. Skin dimpling, nipple retraction or discharge, and large, firm axillary or supraclavicular lymphadenopathy further support malignancy as a possible diagnosis. Tenderness may be present in patients with gynecomastia of less than 6 months' duration, but it is unusual in patients with breast cancer (Table 4).

A thorough testicular exam is essential. When clinical exam suggests a testicular mass or when serum hCG is elevated, testicular ultra-sound (USG) is warranted. Bilaterally small testes imply testicular failure, while asymmetric testes or a testicular mass suggest the possibility of neoplasm. Visual field impairment may suggest pituitary disease. Physical findings of underlying systemic conditions such as thyrotoxicosis, HIV disease, liver, or kidney failure should also be assessed. As obesity is often associated with gynecomastia, body mass index should be documented (56).

Laboratory Evaluation

All patients who present with gynecomastia should have serum testosterone, estradiol, LH, and hCG measured (93) (using an assay that detects all forms of hCG) (Fig 2). Further testing should be tailored according to the history, physical examination and the results of these initial tests. An elevated beta hCG or hCG or a markedly elevated serum estradiol suggests neoplasm and a testicular ultrasound is warranted to identify a testicular tumor. However, non-testicular tumors can also secrete beta hCG or hCG and therefore further imaging such as CT thorax and abdomen is indicated if ultrasound does not show a testicular mass. A low testosterone level, with an elevated LH indicates primary hypogonadism. If the history suggests Klinefelter syndrome, then a karyotype should be performed for definitive

diagnosis. Low testosterone and low LH indicate secondary hypogonadism, and hypothalamic or pituitary causes should be sought. If testosterone and LH are elevated, then the diagnosis of androgen resistance should be considered. In case of estrogen-secreting tumor, LH is usually suppressed with low or low normal testosterone concentrations and negative pituitary imaging. Estradiol concentrations are high. Liver, kidney and thyroid function should be assessed if clinically indicated. Furthermore, if examination of breast tissue suggests malignancy, a biopsy should be performed. This is of particular importance in patients with Klinefelter syndrome, who have an increased risk of breast cancer. On the other hand, if the examination finding is compatible with breast abscess, then fine needle aspiration for microscopy and culture is warranted (60). Acid-fast bacilli and tuberculosis culture can be done if there is risk factor(s) for tuberculosis.

Investigation of gynecomastia

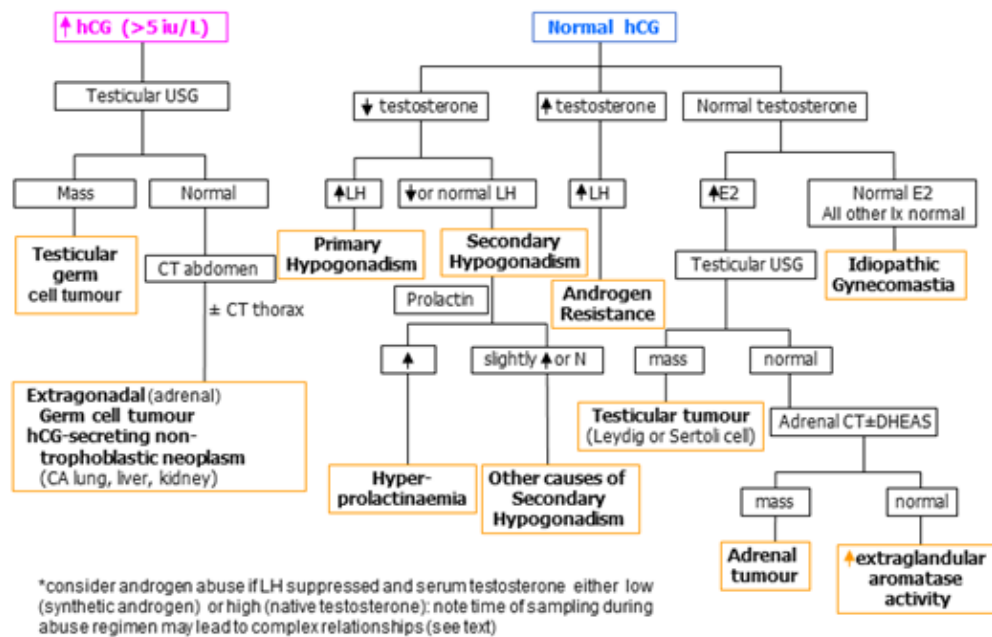


Figure 2. Algorithm for investigation of gynecomastia

TREATMENT

Treatment of the underlying endocrinologic or systemic disease that has caused gynecomastia is appropriate when possible. Testicular tumors, such as Leydig cell, Sertoli cell, or granulosa cell tumors should be surgically removed. In addition to surgery, germ cell tumors are further managed with chemotherapy involving cisplatin, bleomycin, and either vinblastine or etoposide (25, 26). Should underlying thyrotoxicosis, renal, or hepatic failure be discovered, appropriate therapy should be initiated. Medications that cause gynecomastia should also be discontinued whenever possible based on their role in management of the underlying condition. The improvement should be apparent within a month after discontinuation of the culprit drug (61). If the gynecomastia has been present for more than six months, regression is unlikely because of the presence of less reversible fibrotic tissues (62). Of course, if a breast biopsy indicates malignancy, then mastectomy should be performed.

If no pathologic etiology is detected, then appropriate treatment is close observation. A careful breast exam should be done initially every 3-6 months until the gynecomastia regresses or stabilizes, after which a breast exam can be performed yearly. It is important to remember that most cases of pubertal gynecomastia may resolve spontaneously within one to two years, around 20% of patients have residual gynecomastia at the age of 20 (63). An information sheet about gynecomastia is available for those patients who are interested to know more about their conditions (64).

Medical Treatment

If the gynecomastia is severe, does not resolve, of recent onset (less than 6 months) and does not have a treatable underlying cause, some medical therapies may be attempted. There are 3 classes of medical treatment for gynecomastia: androgens (testosterone, dihydrotestosterone, danazol), anti-estrogens (clomiphene citrate, tamoxifen), and aromatase inhibitors such as letrozole and anastrozole.

Once gynecomastia is established, testosterone treatment of hypogonadal men with gynecomastia often fails to produce breast regression. Testosterone treatment may theoretically produce the side effect of gynecomastia by being aromatized to estradiol, but this side effect is uncommon and transient. Having said that, there is limited data to suggest its use to specifically counteract gynecomastia in hypogonadism (65). Dihydrotestosterone, a non-aromatizable androgen, has been used in patients with prolonged pubertal gynecomastia with good response rates but it is not commercially available (66). Danazol, a weak androgen that inhibits gonadotropin secretion, resulting in decreased serum testosterone levels, has been studied in a prospective placebo-controlled trial, whereby gynecomastia resolved in 23 percent of the patients, as opposed to 12 percent of the patients on placebo (67). The dose used for gynecomastia is 200 mg orally twice daily. Unfortunately, undesirable side effects including edema, acne, and cramps have limited its use (24).

Investigators have reported a 64 percent response rate with 100 mg/day of clomiphene citrate, a weak estrogen and moderate anti-estrogen in a cohort study (68). Lower doses of clomiphene have shown varied results, indicating that higher doses may need to be administered, if clomiphene is to be attempted. Tamoxifen, also an anti-estrogen, has been studied in 2 randomized, double-blind studies in which a statistically significant regression in breast size was

achieved, although complete regression was not documented (69). One retrospective study compared tamoxifen with danazol in the treatment of gynecomastia. It was found that patients taking tamoxifen had a greater response with complete resolution in 78 percent of patients treated with tamoxifen, as compared to only a 40 percent response in the danazol-treated group, and the relapse rate was higher for the tamoxifen group (70), though the relapse was not systemically defined and patients with chronic gynecomastia were included. Another prospective cohort study found that 90% of patients taking tamoxifen had successful resolution of their symptoms (89). Although there is a chance of recurrence with cessation of therapy, tamoxifen, due to relatively lower side effect profile and high efficacy, may be a more reasonable choice when compared to the other therapies. If used, tamoxifen should be given at a dose of 10 mg twice or 20 mg daily a day for 3-6 months (24). Responders usually improve with reduced pain within 1 month. Another anti-estrogen, raloxifene, has also been used in the treatment of pubertal gynecomastia but its efficacy needs to be evaluated in randomized prospective studies (71).

An aromatase inhibitor, testolactone, has also been studied in an uncontrolled trial with promising effects (72). Further studies must be performed on this drug before any recommendations can be established on its usefulness in the treatment of gynecomastia. Newer aromatase inhibitors such as anastrozole and letrozole may have therapeutic potential (73, 74), but randomized, double-blind, placebo-controlled trials have not confirmed their efficacy. In a study involving patients receiving bicalutamide therapy for prostate cancer, only tamoxifen, but not anastrozole, significantly reduced the incidence of gynecomastia/breast pain when used prophylactically and therapeutically (75, 76). In another study with pubertal gynecomastia, no significant difference was demonstrated between the anastrozole and placebo

groups in patients suffering from pubertal gynecomastia (77). The use of aromatase inhibitors is notorious for accelerated bone loss in women, but it is uncertain whether the extent of bone loss is similar in adult men (91). Furthermore, men taking anastrozole results in an increase in body fat and decline in sexual function (105).

From various case series, many patients with idiopathic gynecomastia show no significant improvement after medical treatment. The disappointing result may be related to the stage of disease at which medical treatment is initiated. It is likely that many or all of the men who failed to respond to medical therapy had chronic gynecomastia with fibrotic breast tissue that will not change with medical therapy or over time (56, 63). Medical therapy is only used for a short time (up to 6 months) in men with idiopathic and acute (tender, breast tissue present < 6 months) gynecomastia. Tamoxifen has the best evidence for effective medical therapy of acute, idiopathic gynecomastia.

Surgical Treatment

When medical therapy is ineffective, particularly in cases of longstanding gynecomastia, or when the gynecomastia interferes with the patient's activities of daily living, or when there is suspicion of malignancy of breast, then surgical therapy is appropriate. On the other hand, surgical treatment should be postponed in pubertal gynecomastia, after completion of puberty, to minimize the chance of recurrent gynecomastia after surgery (62). Surgery should also be deferred until the underlying cause of gynecomastia has resolved or been treated. Surgical treatment includes removal of glandular tissue coupled with liposuction, if needed, preferably with an individualized approach (78, 79). Nowadays, minimally invasive surgery is available and it may be associated with few complications and prompt recovery (80). If malignancy is suspected,

histological examination is mandatory (56). Use of delicate cosmetic surgical techniques are warranted to prevent unsightly scarring.

PREVENTION OF GYNECOMASTIA IN MEN WITH PROSTATE CANCER

Because androgen deprivation is one of the commonly used treatment modalities for advanced prostate cancer, its possible role in the development of gynecomastia is of particular concern to clinicians. Up to 80% of patients receiving non-steroidal anti-androgen therapy may develop gynecomastia, usually 6-9 months after hormonal treatment. Some patients may have painful and disfiguring gynecomastia (81). Preventive options include tamoxifen, radiation therapy, or aromatase inhibitors.

Tamoxifen is the most effective preventive therapy for gynecomastia due to anti-androgen therapy for treatment of prostate cancer. Tamoxifen is superior to radiotherapy in preventing gynecomastia in patients receiving bicalutamide (Casodex) for prostate cancer in a randomized controlled trial (82). Tamoxifen is superior to aromatase inhibitor to prevent gynecomastia in patients with prostate cancer. For instance, Boccardo, et al. showed that 10% patients in the tamoxifen group (20 mg daily dose) developed gynecomastia, whereas 51% in the anastrozole group

and 73% in the placebo group had gynecomastia over a period of 48 weeks (74). Fradet, et al. showed tamoxifen reduced the incidence of breast events (gynecomastia and/or breast pain) in patients with prostate cancer receiving bicalutamide in a dose-dependent manner (83). Likewise, it has been shown that low dose weekly tamoxifen (20 mg/week) is inferior to the usual dose daily regimen (20mg/day) in terms of the prevention and treatment of gynecomastia (84). Current data suggests tamoxifen 10-20 mg per day is the optimum dose required for prophylaxis of gynecomastia in patients with prostate cancer receiving androgen deprivation therapy (83, 84, 85). Low dose prophylactic irradiation has been reported to reduce the rate of gynecomastia but not breast pain in men receiving estrogens or anti-androgens for prostate cancer (11, 86, 87). Compared with tamoxifen, irradiation seems to be less effective for prevention and treatment of gynecomastia but it is usually well-tolerated (94).

Some studies suggest that the new generation of anti-androgen drugs such as abiraterone acetate, enzalutamide, apalutamide, and darolutamide might be associated with less gynecomastia (88, 95); More recently, it has been reported that 36.6% of patients receiving enzalutamide develop gynecomastia; this incidence seems to be lower than reported in patients who were treated with older anti-androgens such as bicalutamide (99).

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