Review article

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Gynecomastia in adolescent males: current understanding of its etiology, pathophysiology, diagnosis, and treatment

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Gynecomastia (GM) is a common and continuously evolving condition that commonly occurs during adolescence. It is the source of significant embarrassment and psychological stress in adolescent males. GM is characterized by enlargement of the male breast due to the proliferation of glandular ducts and stromal components. The main cause of GM during adolescence is physiological or pubertal GM, which is primarily attributed to an imbalance between estrogen and androgen activity. Physiological GM is typically transient and resolves within several months, although it may take several years to resolve. GM may also be caused by other pathological conditions and could be indicative of an endocrine disease. It is crucial to understand the pathogenesis of GM to distinguish it from normal developmental variants due to pathological causes. The aim of this review is to highlight the significance of GM during adolescence in terms of potential etiologies, clinical and laboratory diagnoses, and current management.

Keywords: Gynecomastia, Obesity, Klinefelter syndrome, Adolescence, Aromatase inhibitors

Highlights

- Gynecomastia (GM) is a common condition that commonly affect males during adolescence .It is primarily attributed to physiological or pubertal causes. However , GM may also be caused by other pathological conditions and could be indicative of an endocrine disease or other medical disorders. The challenge facing endocrinologists lies in their ability to distinguish between physiological and pathologic causes of GM.

Introduction

Gynecomastia (GM) is a condition characterized by the proliferation of glandular tissue in the male breast. It is a clinically significant phenomenon commonly observed in males during adolescence.[1] While physiological or pubertal GM is the most frequently encountered cause during this period, other potential etiologies are uncommon but may arise from various pathological conditions, such as obesity, aromatase excess syndrome (AES), primary or secondary hypogonadism, congenital adrenal hyperplasia, Klinefelter syndrome (KS), testicular feminization syndrome, adrenal and testicular tumors, hyperthyroidism, liver and renal diseases, and malnutrition.[2] Additionally, certain medications have been shown to induce proliferation of male breast tissue.[1]

The challenge facing endocrinologists lies in their ability to distinguish between physiological and pathologic causes of GM. Although studies on the potential causes of GM during adolescence remain limited, some studies have begun to elucidate the subject. For instance, Todorova et al.[3] conducted a retrospective study between 2009 and 2018 in a

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specialized Pediatric Hospital in Sofia, Bulgaria, which involved 157 adolescents with GM after excluding obese adolescents. The authors reported that one-quarter of these cases were due to pathologic conditions, such as hyperprolactinaemia (18 cases, 11.46%), hypogonadotropic hypogonadism (9 cases, 5.73%), hypergonadotropic hypogonadism (8 cases, 5.09%), and prepubertal development (12 cases, 7.64%), while pubertal GM constituted the majority (110 cases, 70.08%) of the total enrolled cases. In this review, we discuss etiology, as well as clinical and laboratory evaluations, and we provide updated management recommendations of GM during adolescence.

Etiology of GM in adolescent boys (Table 1)

1. Physiologic GM in puberty

Physiological or pubertal GM is the most common cause of GM occurring during the adolescent period.[2] Its frequency in this period ranges from 50% to 60%. GM may present as early as age 10, with a peak onset between the ages of 13 and 14 years, before its incidence begins diminishing in late adolescence.[4] Only 10% of males have chronic GM by the age of 17 years.[5] The condition may manifest as a new-onset palpable breast mass with or without mastalgia, or as an accidental finding during a routine physical examination. Despite being primarily bilateral, it can occasionally be unilateral, is frequently asymmetrical, and coincides with Tanner stages 3–4, with the presence of pubic hair and testicular volumes of 5–10 mL.[6] It can be physically uncomfortable and psychologically distressing to the subject, and it may have a negative impact on their self-confidence and body image.[7]

Most cases of pubertal GM are assumed to be caused by an imbalance between the activities of the hormones estrogen and androgen in the breast tissue.[8] Pubertal GM is caused by either increased estrogen production, decreased testosterone production, or a combination of both.[4] The antiestrogenic activity of testosterone has a generalized suppressive impact on the growth and differentiation of breast tissue, whereas estrogen has a stimulatory and proliferative effect on ductal and glandular tissue in the breast.[9] Involution and atrophy of the ducts occur as a result of rising androgen levels in the blood as puberty progresses.[4] However, some studies have indicated that a significant number of adolescents with pubertal GM had normal estrogen level, and they linked GM to increased susceptibility of the breast tissue to normal level of circulating estrogen. These studies also claimed that the presence of local tissue factors in the breast increased the aromatization of androgens to estrogen in the breast tissue itself, which was corroborated by the presence of elevated aromatase activity in the fibroblasts in the pubic skin of GM patients.[5,8] Furthermore, puberty is the time of the fastest linear development in children, as evidenced by peak height velocity, when levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are at their highest. Through their respective receptors found in the breast, GH and IGF-1 both promote linear growth and breast tissue proliferation.[10] Moreover, one study found that nearly half of the adolescents with this condition reported a positive family history, suggesting that genetics may play a part in the pathogenesis of GM.[1]

Table 1. Etiology of gynecomastia (GM) during adolescence

1. Physiologic GM of puberty
2. Obesity
3. Aromatase excess syndrome
4. Drugs and herbal medicine
Drugs: spironolactone, alkylating drugs, anabolic-androgenic steroids, human chorionic gonadotropin, ketoconazole, cimetidine, and androgen inhibitors
Herbal medicine: lavender, tea tree oil, angelica polymorphea varsinensis
5. Environmental factors: air pollution, radiation, organochlorine pesticides, plastics, plasticizers, fuels, polycyclic aromatic hydrocarbons, and consumer products
6. Chronic diseases: cystic fibrosis, ulcerative colitis, liver disease, chronic renal failure, and human immunodeficiency virus
7. Klinefelter syndrome
8. Congenital adrenal hyperplasia
9. Hyperthyroidism
10. Hyperprolactinemia
11. Primary gonadal failure
12. Testicular feminization syndrome
13. Diabetic mastopathy
14. Testicular tumors
15. Feminizing adrenocortical tumors
16. Breast cancer

2. Obesity

Today's increasing level of obesity is associated with increased breast adipose tissue. This latter increase may lead to pseudogynecomastia, which might not be associated with true GM.[8] A study reported that men with a body mass index (BMI) of 25 kg/m^2 or higher are far more likely to develop GM or pseudogynecomastia, with a reported prevalence as high as 80%.[11] Additionally, both GM and breast diameter are positively associated with high BMI in both adolescents and adults.[12] A study conducted between 1997 and 2008 screened a database for young male "breast" specimens. Of the 69 patients identified, 51% were classified as obese based on BMI, 16% were overweight, and 33% had a normal weight.[13] Individuals who are obese are prone to GM due to their higher concentration of adipose tissue in the breast region. This adipose tissue is known to contain the aromatase enzyme complex, which facilitates the conversion of testosterone to estradiol.[14] Furthermore, circulating leptin is implicated in the development of GM in obese adolescents through an increase in estrogen and/or the estrogen/androgen ratio via stimulation of the leptin effect on aromatase enzyme activity in both adipose and breast tissues, through a direct growth-stimulating effect on mammary epithelial cells and/or increases in the sensitivity of breast epithelial cells to estrogen.[15]

3. Aromatase excess syndrome

AES is a rare genetic disease characterized by pre- or peri-pubertal onset of GM and is transmitted as an X-linked recessive or autosomal dominant trait.[16] This condition is most likely caused by a genetic defect in the 5'-end of the P450 aromatase gene. This single gene mutation results in an increase in the production and activity of the aromatase enzyme CYP19, a crucial enzyme in the synthesis of estrogen and the conversion of androgen to estrogen. Excess activity of this enzyme is linked to a 100-fold increase in extraglandular aromatization in peripheral tissues, which increases estrogen production.[17] Additional symptoms of excess estrogen include rapid bone growth during puberty, which reduces adult height; hypogonadotropic hypogonadism; a high-pitched voice; and sparse facial hair.[16]

4. Drugs and herbal medicine

GM can develop as a result of exposure to medications that lower the level of androgens, increase estradiol levels, or displace androgens from breast androgen receptors. Spironolactone, alkylating drugs, anabolic-androgenic steroids, human chorionic gonadotropin (hCG), ketoconazole, cimetidine, and androgen inhibitors such as flutamide are all associated with the development of GM.[18]

Herbal medicine has also been implicated in the development of GM. Henley et al.[19] documented 3 cases of prepubertal GM that were temporally linked to the use of skin and hair products containing lavender and tea tree oil. Similarly, *Angelica polymorphea varsinensis* (also known as "Dong Quai"), an herb used to treat gynecological diseases, has also been linked to the development of GM.[20]

5. Environmental factors

The development of GM may theoretically be induced by ongoing environmental exposure to chemicals that have a mild estrogen-agonist effect. Air pollution, radiation, organochlorine pesticides, plastics, plasticizers, fuels, polycyclic aromatic hydrocarbons, and consumer products that contain endocrine disrupting chemicals are just a few substances in this category.[21]

6. Chronic diseases

GM has been linked to chronic illnesses such cystic fibrosis, ulcerative colitis, liver disease, chronic renal failure, and human immunodeficiency virus (HIV). Liver cirrhosis is usually associated with low serum testosterone level and increased estradiol level. Patients with chronic renal failure are frequently hypogonadal, experiencing defects in testicular steroidogenesis, and many of them develop GM. In patients with HIV, GM occurs in 2%–3% and is triggered either by lipodystrophy or by highly active antiretroviral therapy.[1,2,8,22]

7. Klinefelter syndrome

According to reports, more than 50% of KS patients have GM as a result of both increased aromatase activity and decreased androgen production.[23] A euchanoid body habitus; delayed development of secondary sexual features; thin facial and pubertal hair; and small, firm testes are typical features of KS when it manifests in adolescence.[24]

8. Congenital adrenal hyperplasia

GM is uncommon in males with 11-hydroxylase deficiency[25] and is extremely unusual in children with 21-hydroxylase deficiency.[26] Accelerated growth and virilization are linked to GM in these conditions.[25,26]

9. Hyperthyroidism

Graves disease (GD) is a contributing factor to hyperthyroidism in adolescents. In most cases, GM is not the primary indicator of GD owing to early diagnosis. Severe hyperthyroidism can escalate serum sex hormone-binding globulin (SHBG) level.[27] The decreased affinity of estradiol to SHBG compared to testosterone can lead to an increase in the ratio of free estradiol to free testosterone, resulting in clinically apparent GM.[28]

10. Hyperprolactinemia

Prolactin-producing pituitary adenomas (prolactinomas) induce GM via their indirect role in change of the androgen/estrogen ratio. However, not all patients with prolactinomas develop GM, and most GM patients do not have elevated serum prolactin level.[29]

11. Primary gonadal failure

Testicular trauma, mumps, orchitis, and chemotherapy can all result in primary gonadal failure, which lowers serum testosterone level, increases lutenizing hormone (LH) level, and stimulates Leydig cells to produce estrogens, resulting in GM.[1,2,30]

12. Testicular feminization syndrome

Testicular feminization syndrome is commonly associated with the development of female breast appearance in males with an XY karyotype as a result of gonadal estrogen production.[2,4,31]

13. Diabetic mastopathy

Patients with type 1 diabetes who have had the condition for a long time may develop diabetic mastopathy (DMP), presenting as hard, diffuse enlargements in one or both breasts.[32] The

exact cause of DMP remains unknown, but the condition is believed to be a type of auto-immune reaction. Some theories suggest that exogenous insulin can cause an inflammatory or immunologic reaction that can result in the development of GM in DMP.[33]

14. Testicular tumors

GM without testicular swelling is the main symptom in 7%–11% of subjects with testicular tumors, and it may be the only clinical finding on physical examination at the time of diagnosis.[34] Sertoli or Leydig cell tumors, which are benign testicular tumors, produce a high estradiol level, which increases the blood concentration of SHBG and selectively binds testosterone to reduce the level of free testosterone, which leads to GM. It is important to underscore the need for testicular examination, particularly in young patients who present with GM. Some specialists recommend routine testicular ultrasonography for all patients who present with GM, even if no abnormalities are found on a testicular examination.[35]

15. Feminizing adrenocortical tumors

Feminizing adrenocortical tumors (FATs) are extremely rare and have a median age at diagnosis of 6 years. FATs are typically malignant in adults, but approximately half of them are benign in children. In boys, GM is the most common symptom, present in 98% of cases. This is attributed to tumor secretion of large amounts of androstenedione, which is converted into estrone by peripheral tissue aromatase.[3,36,37]

16. Breast cancer

Breast cancer in adolescents accounts for 0.1% of all breast cancer cases and less than 1% of all pediatric cancer cases.[38] Patients with KS have a 20- to 50-fold greater risk of developing breast cancer.[39] A family history of BRCA2-positive breast cancer greatly increases the risk of male breast cancer among mutation carriers, as do hyperestrogenic circumstances such as obesity, alcohol use, and past exposure to exogenous estrogen.[40] Breast carcinoma usually consists of a unilateral hard irregular mass, located outside the areola, and it may be accompanied by skin dimpling, nipple retraction, and axillary lymphadenopathy. Ultrasonography is the preferred imaging modality as it can identify lesions in dense breast tissue and avoid radiation exposure.[38]

Evaluation of adolescent males with GM (Table 2)

For all adolescents presenting with GM, a detailed history and physical examination should be performed to differentiate pathologic from pubertal GM.

1. History

A detailed medical history should include the onset and duration of breast enlargement, pain or tenderness, presence of nipple discharge or overlying skin changes, undervirilization, and testicular swelling or masses. Past medical history should focus on undescended testes, viral infection (i.e., mumps), and liver or renal disease,[34] as well as male relatives who have long-term or permanent GM.[3,8] A thorough review of all recent medications, including herbal remedies, illegal substances, and anabolic steroids, should be conducted. To investigate any potential usage of illegal drugs or anabolic steroids, the teen should be interviewed alone.[18] A psychological evaluation and a mental health screen should be a part of the assessment.[3]

2. Examination

The general exam should include anthropomorphic measurements, including height, weight, BMI, and upper and lower body segment measurements; as well as genital examination for signs of virilization, Tanner staging, testicular volume, and testicular masses.[1,2,30] The breast examination should note the consistency of the breast tissue, presence of breast mass, and any overlying skin changes, nipple discharge, and axillary lymphadenopathy.[3,14,15] It is important to distinguish between true GM, characterized by a discreet disc of palpable glandular tissue under the nipple-areolar complex, and pseudogynecomastia (fatty breasts), which is commonly observed in obese males and is characterized by more diffuse adiposity of the anterior chest wall without glandular proliferation.[11,41]

Table 2. Work up of GM in adolescents

History
• Onset, course duration, unilateral or bilateral location
• Chronic disease
• Recent medications, supplements and herbal remedies
• Family history
• Psychological evaluation
Physical examination
• Anthropomorphic measurements (weight, height, and body mass index)
• General examination (signs of systemic illnesses)
• Genital examination (testicular volume, and mass)
• Breast examination (rule out pseudogynecomastia)
Investigations
The choice of tests is influenced by the clinical picture
• Routine laboratory tests
• Hormonal profile: FSH, LH, estradiol, testosterone, DHEA-S, hCG, TSH, and prolactin
• Karyotyping
• Testicular and adrenal ultrasound

GM, gynecomastia; FSH, follicle-stimulating hormone; LH, luteinizing hormone; DHEA-S, dehydroepiandrosterone-sulfate; hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone.

3. Investigations

The choice of laboratory or radiological tests for evaluation of GM is influenced by the clinical picture. In the absence of abnormalities suggestive of potentially pathologic causes of GM on history or physical examination, neither laboratory nor radiographic studies are recommended for adolescents with GM.[3] However, prepubertal age, under- or overviralization, an eccentric breast mass, rapid progression of breast enlargement, a testicular mass, or persistence beyond the usual observation period (12–18 months) demands a further workup.[8] Evaluation of liver, renal, and thyroid function is indicated for boys who appear chronically ill.[22] Karyotyping is necessary if the testes are less than 3 cm in length or 6 mL in volume to rule out KS.[23] Adolescent boys with signs of hypogonadism, precocious puberty, or macrogynecomastia should undergo measurement of LH, follicular stimulating hormone, estradiol, testosterone, dehydroepiandrosterone sulfate (DHEA-S), hCG, and prolactin, especially if galactorrhea is associated with the clinical picture.[22] A high DHEA-S level that is well beyond that observed in adrenarche requires adrenal ultrasound. Moreover, a high estradiol level may require hepatic, adrenal, and testicular ultrasound.[34,35] A high hCG level warrants magnetic resonance imaging of the brain, chest, abdomen, and testes to search for an hCG-secreting tumor.[8,22] Breast ultrasound is not usually recommended unless it is uncertain if the breast mass is GM.[38] Neither mammography nor fine-needle aspiration are recommended in the diagnostic evaluation of adolescent GM.[38-40]

Management of adolescents with GM (Table 3)

The management of GM necessitates the consideration of secondary etiologies. Addressing underlying malnutrition; cirrhosis; hyperthyroidism; hypogonadism; and excision of testicular, adrenal, or other responsible tumors may result in regression of GM.[30] In cases of drug-induced GM, cessation of the offending agent or substitution with alternative medication is recommended.[1,2,9,22]

Table 3. Management of gynecomastia (GM) in adolescent boys

1. Secondary causes should be treated and offending drugs should be discontinued
2. Observation and reassurance are the appropriate management approach for pubertal GM
3. Pharmacological treatment
Pharmacological intervention may be considered for cases of pubertal GM that do not resolve spontaneously within a period of 2 years.
Antiestrogenic agents: such as tamoxifen is associated with a favorable safety profile , well-tolerated and effective for recent-onset and tender GM
Androgens: such as danazol and aromatase inhibitors such as anastrozole may have some benefit
4. Surgical treatment
It is indicated in nonobese male adolescents with longstanding GM when medical therapy is ineffective.
Surgery is offered towards the end of puberty
Subcutaneous mastectomy technique is the most frequently employed method

1. Pharmacological treatment

Pharmacological intervention may be considered for cases of pubertal GM that do not resolve spontaneously within a period of 2 years or for those associated with significant tenderness or psychosocial morbidity. However, given that pubertal GM is a transient and self-limiting condition that resolves spontaneously in more than 90% of cases within 3 years, observation and reassurance are generally regarded as the most appropriate management approach. Medical intervention is most effective during the painful phase of GM.[42]

Presently, the U.S. Food and Drug Administration has not sanctioned any pharmacological interventions for the management of pubertal GM. The primary impediment in investigating pharmacotherapeutic approaches in treating pubertal GM is the difficulty in quantifying treatment effect owing to the natural history of spontaneous regression in the majority of adolescents. Furthermore, medical interventions are likely to be efficacious when employed during the early proliferative phase, before glandular structural transformation into stromal hyalinization and fibrosis. A plethora of medications has been employed for the treatment of GM, with the objective of resolving the estrogen-androgen imbalance through 3 potential pathways of antiestrogens, androgens, and aromatase inhibitors.[43]

Antiestrogenic agents, such as tamoxifen, have been subjected to extensive medical investigation as a therapeutic option for GM. This treatment modality is associated with a favorable safety profile and is relatively nontoxic and well-tolerated.[42] Furthermore, tamoxifen rapidly alleviates associated tenderness, making it a primary treatment option for cases of acute GM that fail to resolve spontaneously and are symptomatic.[43] Tamoxifen treatment results in the resolution of palpable breast tissue in most patients (86%–100%), with no serious adverse effects reported.[44] However, existing studies are limited by small sample sizes and the lack of a placebo control group.[45]

Androgens, such as danazol, have been shown to exert weak androgenic effects by inhibiting estrogen production through the suppression of pituitary secretion of gonadotropins.[8,46] Despite its efficacy in managing GM, the use of danazol is limited owing to its potential for adverse effects, including weight gain.[43] Topical preparations may be preferred over injectable forms, as they result in more consistent level of testosterone in the body and may mitigate the risk of aromatization to estradiol and exacerbation of breast enlargement.[46]

Aromatase inhibitors, such as anastrozole, are known to inhibit the activity of aromatase and subsequently reduce the levels of estrogen in both the periphery and mammary tissue.[42] The effectiveness of anastrozole, a potent aromatase inhibitor used for treating pubertal GM, has been investigated in 3 studies. While 2 observational studies with small samples

have shown promising results for the use of anastrozole, a well-designed randomized controlled trial of 80 pubertal boys has demonstrated that anastrozole is not significantly more effective than the placebo in reducing the breast volume calculated from ultrasonography measurements (38.5% vs. 31.4%, P=0.47).[8,47]

2. Surgical treatment

The decision to perform surgical treatment should be tailored to each patient's specific circumstances. In nonobese male adolescents presenting with persistent breast enlargement, surgical treatment may be considered after a period of observation of at least 12 months; in the presence of breast pain or tenderness, significant psychosocial distress, lack of tolerance, or failure of medical treatment; or for cosmetic reasons requiring tissue removal. Surgery is offered toward the end of puberty.[8,42] The primary objectives of surgical treatment for GM are to restore normal chest contours, eliminate the infra-mammary fold, correct the position of the nipple-areola complex, remove redundant skin, create symmetry between the 2 halves of the chest, and minimize scarring. Various techniques exist for correction of GM, with a wide range of excisional and liposuction procedures.[30,48] The subcutaneous mastectomy technique is the most frequently employed method. It involves direct removal of glandular tissue through a periareolar or transareolar approach, with or without adjunctive liposuction. For cases that are more advanced, skin resection becomes necessary.[3,42]

Conclusions

GM, a prevalent and clinically significant condition among males during adolescence, is primarily attributed to physiological or pubertal causes. Nevertheless, other pathological conditions may contribute to GM. Identifying patients with underlying pathological conditions is crucial, and can be achieved through a comprehensive medical history, clinical examination, and laboratory tests as appropriate. In cases of pubertal GM that persist for more than 2 years or are associated with significant tenderness or psychosocial morbidity, pharmacological intervention may be considered. Surgical treatment, on the other hand, is indicated in cases where medical treatment fails, the condition is intolerable, persistent psychosocial distress is experienced, or for cosmetic purposes.

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