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Gynecomastia - a literature review of management, diagnosis and treatment

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Abstract

Introduction and Purpose: Gynecomastia is a common clinical problem that can also be a symptom of many serious disorders. The aim of this study is to analyze the etiology, pathogenesis, diagnostics, as well as pharmacological and surgical treatment, while also addressing the psychological aspect of the condition.

State of Knowledge: Gynecomastia is the development of noncancerous breast tissue in males. It can occur unilaterally or bilaterally and may cause pain. It can be a natural occurrence during infancy, adolescence, and and in older age. It is usually accompanied by an imbalance between estrogens and androgens. Hormonal disorders lead to the growth of stromal and ductal proliferation. In the diagnostic process, the most important aspect is establishing the cause of the condition, allowing for the implementation of appropriate treatment. Gynecomastia can cause a decrease in quality of life, depression, anxiety, and reduced self-esteem.

Conclusions: Gynecomastia is a complex condition that requires an individualized approach to the patient. It can be a side effect of medication use, result from an underlying disease, or occur idiopathically. Surgical treatment forms the basis of the therapeutic process. Currently, combined surgical techniques are most commonly used to achieve the best cosmetic effect.

Keywords: gynecomastia, hormonal imbalance, adolescent gynecomastia, hormonal treatment

INTRODUCTION

Gynecomastia is a noncancerous enlargement of the breast gland tissue in males. It can occur unilaterally or bilaterally and cause significant pain [1,2]. Physiologically, gynecomastia most commonly occurs in three age groups: infancy, puberty, and older age [2]. It is typically suspected during a physical examination and should be differentiated from other conditions, such as pseudogynecomastia, which is defined as breast enlargement due to the proliferation of fatty tissue within the breast [3]. Gynecomastia can negatively impact the quality of life and cause distress [4]. In this article, the authors aim to provide an understanding of the specifics of this condition and discuss aspects related to its diagnosis and treatment.

HISTOLOGY

It has been acknowledged that the primary cause of breast enlargement is the growth of the stroma, accompanied by varying degrees of ductal proliferation. The significant stromal changes include increased blood vessel formation, proliferation of fibroblasts, deposition of

collagen fibers, and hyalinization [5]. The observed histological changes may vary depending on the patient's age and the duration of the disease [6].

PHYSIOLOGICAL GYNECOMASTIA

Physiologically, gynecomastia can occur in three age groups. Firstly, during the early stages of life when newborns are still exposed to the influence of estrogens derived from the conversion of dehydroepiandrosterone and dehydroepiandrosterone sulfate in the placenta. The next period with a significant increase in the occurrence of gynecomastia is during adolescence. The mechanism behind this phenomenon is not fully understood. In some patients, both estrogen and testosterone levels are normal, while in others, the concentration of free testosterone is decreased. In older men, glandular tissue enlargement is observed primarily due to increased adipose tissue. In this tissue, androgens are converted to estrogen by the aromatase enzyme. Elevated aromatase levels may be responsible for increased estrogen production and reduced degradation [1-3].

The estimated prevalence during adolescence ranges from 48% to 64% [7]. The highest percentage of patients suffering from this condition is found in the 13-14 age range [2,3,7].

PATHOLOGICAL GYNECOMASTIA

In the case of pathological gynecomastia, the majority of causes are considered idiopathic [8]. Gynecomastia is largely a result of disorders that disrupt the balance between estrogens and androgens. Breast glands have receptors for both hormones, with estrogens promoting proliferation and androgens inhibiting it [9]. Therefore, an imbalance between them can lead to pathological tissue growth [10].

This can occur due to an increase in estrogen levels, which can happen through various mechanisms such as increased production, accumulation in the serum, or local tissue accumulation [11].

Such an increase can also be a result of a neoplastic process. Tumors such as Sertoli cell tumors, adrenal tumors, or Leydig cell tumors can cause overproduction of estrogens or their precursors. Although these tumors are relatively rare, they should always be considered in the diagnosis of gynecomastia.

Adrenal tumors can contribute to the overproduction of dehydroepiandrosterone and androstenedione, both of which can undergo peripheral aromatization into estrogens.
Serum free testosterone levels are decreased in patients with androgen deficiency, such as Klinefelter syndrome, testicular damage, or after castration. This also occurs in secondary hypogonadism associated with pituitary or hypothalamic disease [12].

In adipose tissue, the action of aromatase leads to the conversion of testosterone to estrogens. Therefore, increased expression and activity of aromatase contribute to the development of gynecomastia. This process is crucial in estrogen production in males, which is why the condition is more common in obese men [13].

THYROID HORMONES

Thyroid hormones have an impact on the hormonal balance of other tissues. Deficiency or excess of these hormones may be associated with an increased risk of gynecomastia.
Hyperthyroidism leads to an increase in sex hormone-binding globulin (SHBG). With a higher affinity for testosterone, SHBG reduces the concentration of free testosterone, resulting in an increase in free estrogen. Gynecomastia can be the initial manifestation of thyroid hormone excess [14,15].

Hypothyroidism has also been associated with the occurrence of gynecomastia. These patients may experience a decrease in testosterone levels. This is likely due to an increase in prolactin secretion in response to elevated thyroid-releasing hormone [16].

DRUG-INDUCED GYNECOMASTIA

Approximately 20% of gynecomastia cases are attributed to medication use [17]. Among them, the most commonly mentioned medications are antiandrogens, antiretrovirals, first-generation antipsychotics, antihypertensive drugs, and estrogen hormone therapy. These medications can have varying effects on the hormonal balance of the body, potentially leading to gynecomastia as a side effect.

One example is the increase in prolactin caused by antipsychotic medications (such as olanzapine, haloperidol, and risperidone). Elevated prolactin levels result in a decrease in gonadotropin, which consequently leads to a reduction in estrogen and androgens [18].

Gynecomastia is a known side effect among patients taking spironolactone. Its occurrence is dependent on the duration of the disease and the dosage of the medication. The estimated prevalence is approximately 10% of cases. The mechanism responsible for this phenomenon involves a decrease in testosterone production and an increase in peripheral conversion to estradiol [19].

OTHER CONDITIONS

Several medical conditions can have systemic effects and thus impact hormonal balance. Conditions contributing to malnutrition and wasting can contribute to the occurrence of gynecomastia. Among these conditions, chronic renal failure, liver disease, and ulcerative colitis are mentioned. The problem most commonly arises with nutritional deficiencies, which lead to increased hormonal production [2]. Gynecomastia can be caused by liver cirrhosis, which is a relatively common occurrence. Within the liver, breakdown of estrogen takes place, and if its function is compromised, it can lead to elevated levels of estrogen [20]. Elevated uricemia in patients with renal failure can directly damage the testes, leading to decreased testosterone levels through LH and FSH stimulation [21].

DIAGNOSTICS

Due to the wide range of possible causes of gynecomastia, a detailed diagnosis should be undertaken.

The first step in diagnosing gynecomastia is typically to gather a detailed medical history from the patient. It is crucial to determine the timing of when the changes were first observed and if there were any accompanying symptoms [22]. The medical history should be further expanded to include information about liver, kidney, and adrenal gland disorders, as well as past or current hormonal problems. Information about family history, genetic disorders, or medications taken is crucial for the course of treatment.

The next step is a physical examination. Palpable, symmetrical, firm masses located subareolarly may indicate the growth of glandular tissue. It is most commonly observed bilaterally, although it may not be symmetrical [23]. Tissue growth can occur unilaterally; however, this is much less frequently observed [3].

Considering the differential diagnosis, several significant conditions should be considered. One of the first is pseudogynecomastia, which is breast enlargement due to an increase in fatty tissue. In the physical examination, there is no palpable firm tissue [24].

The second differentiating condition should be breast cancer. When differentiating these diseases, particular attention should be paid to the nipple and its surroundings. Typically, malignant lesions are localized unilaterally, and discharge, blood, or retracted nipple may be observed [25]. Although rare in men, special attention should be paid to patients with Klinefelter syndrome. These patients have a 20-50 times increased risk of breast cancer. Other risk factors for male breast cancer include family history, BRCA gene mutation, previous radiation therapy, or hyperprolactinemia [26].

If difficulties arise in making a diagnosis, further diagnostic tests should be considered. Among the available imaging diagnostics, ultrasound, and mammography are the most commonly chosen, and magnetic resonance imaging, although rare, can be an additional tool. In case of suspicion of a neoplastic process, a biopsy performed under ultrasound guidance will be required [27].

TREATMENT

Gynecomastia is usually a self-limiting condition. In the absence of significant underlying pathology, regular follow-up examinations are recommended. If drug-induced gynecomastia is diagnosed, the medications should be discontinued, and appropriate treatment for the underlying condition should be initiated.

In the case of gynecomastia in newborns, symptoms typically resolve within approximately 2-3 weeks, while among teenagers, this duration is considered to be around 18 months [28,3]. It is important to consider the psychological discomfort associated with this condition. In the case of significant distress related to the presence of gynecomastia, pharmacological treatment

or surgical correction should be considered. Due to the progressive replacement of glandular tissue, pharmacological treatment achieves the highest effectiveness when initiated as early as possible after the onset of symptoms. Surgical treatment is not limited by the duration of symptoms [29].

PHARMACOLOGICAL TREATMENT

Pharmacological treatment of gynecomastia is limited and aims to restore the balance between estrogens and androgens.

Tamoxifen, with its antiestrogenic activity, blocks estrogen receptors and inhibits its proliferative effect on breast glandular tissue [30,31]. It is presumed to be effective in cases of idiopathic gynecomastia or iatrogenic gynecomastia [32]. Potentially, tamoxifen could be used in the treatment of pubertal gynecomastia, but there is insufficient evidence to support this [33].

Raloxifene, being a selective estrogen receptor modulator, is conventionally used in postmenopausal osteoporosis in women. Its use in gynecomastia is not sufficiently studied. Reduction of breast glandular tissue has been observed in some cases when used on a small group of patients with pubertal gynecomastia. No side effects were observed, and the authors leaned towards stating that raloxifene treatment is effective and safe in patients with pubertal gynecomastia [34].

The use of danazol in the pharmacological treatment of gynecomastia has been proposed before. It is a steroidal analog that inhibits the pulsatile secretion of gonadotropin-releasing hormone and subsequently luteinizing hormone and follicle-stimulating hormone. It also exhibits antiestrogenic effects by increasing free testosterone levels through the inhibition of sex hormone-binding globulin (SHBG) secretion. Jones et al. [35] observed less severe breast tenderness and a decrease in the mean diameter of the lump in the group receiving danazol compared to the control group.

Anastrozole exhibits a different mechanism of action compared to the aforementioned drugs. Being an aromatase inhibitor, it may be a therapeutic option among patients with pubertal gynecomastia. However, its use in gynecomastia needs to be further investigated due to very limited literature confirming its effects [36].

Establishing a conclusive pharmacological strategy for treating gynecomastia is difficult because there is a lack of comprehensive scientific studies and documented instances [37].

SURGICAL TREATMENT

Surgical intervention may be indicated in cases of proliferative changes that do not respond to pharmacological treatment or when gynecomastia has persisted for a long duration, leading to the formation of fibrous tissue. If gynecomastia persists for a duration of 2 years, the chances of spontaneous regression decrease progressively [38].

The surgical techniques commonly used in the treatment of gynecomastia include excision of glandular tissue, liposuction, skin resection, or a combination of these techniques [39].

Given the multiple inadequacies of pharmacological intervention, surgical correction stands as the fundamental aspect of addressing gynecomastia. The most commonly used technique is subcutaneous mastectomy, which involves the removal of glandular tissue, typically through an areolar incision [40].

Liposuction, which involves the removal of fatty tissue, is often performed in conjunction with a mastectomy [10].

In some patients, excess skin tissue may be significant, usually accompanied by an enlarged nipple areola. The decision to perform skin resection should be considered on an individual basis. Younger patients generally have greater regenerative capabilities, so the primary corrective surgery usually focuses on reducing glandular tissue. The decision to remove excess skin is typically made within one year of the initial surgery [41].

In most cases, individuals with gynecomastia benefit from a combination of techniques involving the removal of both glandular and fatty tissue. Opting for a combined procedure generally leads to superior cosmetic results [42].

PSYCHOLOGICAL ASPECT

The impact of gynecomastia on behavior and daily life is significant. However, this aspect of the condition may be overlooked in the therapeutic process.

Gynecomastia has a significant negative influence on the well-being and psychological health of the patient. It can greatly affect social relationships, and the behaviors chosen by patients, and limit their daily activities. Being frequently present during adolescence, it also causes considerable psychological discomfort associated with negative perceptions by peers [43]. Limitations in daily activities resulting from the condition can also lead to a decrease in physical activity. Such behavior has an additional negative impact due to the potential

increase in adipose tissue, which creates the potential for further imbalances in hormone levels between estrogens and androgens [44].

CONCLUSIONS

Gynecomastia is a complex disease, and thus requires such an approach. Patient care should be provided by an interdisciplinary team for this reason. Correction of gynecomastia is possible, and the basis of this process is to determine the cause. It may manifest itself as a side effect of previously used treatment or as a symptom of underlying disease. With this in mind, an in-depth analysis of each patient is necessary at the beginning of the therapeutic process. The modern approach allows to offer patients several options, mainly based on various surgical methods. The process of selecting the best strategy is complicated and dependent on numerous aspects. In everyday practice, it is important to remember that individuals having this condition frequently experience psychological problems in addition to physical manifestations. The treatment option should be as individual as possible.

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REFERENCES

1. Nordt CA, DiVasta AD. Gynecomastia in adolescents. Curr Opin Pediatr. 2008 Aug;20(4):375-82. doi: 10.1097/MOP.0b013e328306a07c. PMID: 18622190.
2. Lemaine V, Cayci C, Simmons PS, Petty P. Gynecomastia in adolescent males. Semin Plast Surg. 2013 Feb;27(1):56-61. doi: 10.1055/s-0033-1347166. PMID: 24872741; PMCID: PMC3706045.
3. Cuhaci, Neslihan; Polat, Sefika Burcak; Evranos, Berna; Ersoy, Reyhan; Cakir, Bekir. Gynecomastia: Clinical evaluation and management. Indian Journal of Endocrinology and Metabolism 18(2):p 150-158, Mar–Apr 2014. | DOI: 10.4103/2230-8210.129104
4. Ordaz DL, Thompson JK. Gynecomastia and psychological functioning: A review of the literature. Body Image. 2015 Sep;15:141-8. doi: 10.1016/j.bodyim.2015.08.004. Epub 2015 Sep 24. PMID: 26408934.
5. Nicolis GL, Modlinger RS, Gabrilove JL. A study of the histopathology of human gynecomastia. J Clin Endocrinol Metab. 1971 Feb;32(2):173-8. doi: 10.1210/jcem-32-2-173. PMID: 5539033.
6. Fricke A, Lehner GM, Stark GB, Penna V. Gynecomastia: histological appearance in different age groups. J Plast Surg Hand Surg. 2018 Jun;52(3):166-171. doi: 10.1080/2000656X.2017.1372291. Epub 2017 Sep 6. PMID: 28876176.
7. Gikas P, Mokbel K. Management of gynaecomastia: an update. Int J Clin Pract. 2007 Jul;61(7):1209-15. doi: 10.1111/j.1742-1241.2006.01095.x. Epub 2007 Mar 16. PMID: 17362482.
8. Wollina U, Goldman A. Minimally invasive esthetic procedures of the male breast. J Cosmet Dermatol. 2011 Jun;10(2):150-5. doi: 10.1111/j.1473-2165.2011.00548.x. PMID: 21649820.
9. Vandeven HA, Pensler JM. Gynecomastia. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430812/
10. Johnson RE, Murad MH. Gynecomastia: pathophysiology, evaluation, and management. Mayo Clin Proc. 2009 Nov;84(11):1010-5. doi: 10.1016/S0025-6196(11)60671-X. PMID: 19880691; PMCID: PMC2770912.
11. Mathur R, Braunstein GD. Gynecomastia: pathomechanisms and treatment strategies. Horm Res. 1997;48(3):95-102. doi: 10.1159/000185497. PMID: 11546925.

12. Swerdloff RS, Ng JCM. Gynecomastia: Etiology, Diagnosis, and Treatment. [Updated 2023 Jan 6]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-.
13. Braunstein GD. Aromatase and gynecomastia. Endocr Relat Cancer. 1999 Jun;6(2):315-24. doi: 10.1677/erc.0.0060315. PMID: 10731125.
14. Gordon DL, Brown JL, Emanuele NV, Hall L 3rd. Gynecomastia as the initial manifestation of hyperthyroidism. Endocr Pract. 1997 Mar-Apr;3(2):80-1. doi: 10.4158/EP.3.2.80. PMID: 15251481.
15. Sanyal T, Dutta D, Shivprasad K, Ghosh S, Mukhopadhyay S, Chowdhury S. Gynaecomastia as the initial presentation of thyrotoxicosis. Indian J Endocrinol Metab. 2012 Dec;16(Suppl 2):S352-3. doi: 10.4103/2230-8210.104089. PMID: 23565425; PMCID: PMC3603073.
16. Kanakis GA, Nordkap L, Bang AK, Calogero AE, Bártfai G, Corona G, Forti G, Toppari J, Goulis DG, Jørgensen N. EAA clinical practice guidelines-gynecomastia evaluation and management. Andrology. 2019 Nov;7(6):778-793. doi: 10.1111/andr.12636. Epub 2019 May 16. PMID: 31099174.
17. Bowman JD, Kim H, Bustamante JJ. Drug-induced gynecomastia. Pharmacotherapy. 2012 Dec;32(12):1123-40. doi: 10.1002/phar.1138. Epub 2012 Nov 16. PMID: 23165798.
18. Roke Y, van Harten PN, Boot AM, Buitelaar JK. Antipsychotic medication in children and adolescents: a descriptive review of the effects on prolactin level and associated side effects. J Child Adolesc Psychopharmacol. 2009 Aug;19(4):403-14. doi: 10.1089/cap.2008.0120. PMID: 19702492.
19. Haynes BA, Mookadam F. Male gynecomastia. Mayo Clin Proc. 2009 Aug;84(8):672. doi: 10.1016/S0025-6196(11)60515-6. PMID: 19648382; PMCID: PMC2719518.
20. Dickson G. Gynecomastia. Am Fam Physician. 2012 Apr 1;85(7):716-22. PMID: 22534349.
21. Karagiannis A, Harsoulis F. Gonadal dysfunction in systemic diseases. Eur J Endocrinol. 2005 Apr;152(4):501-13. doi: 10.1530/eje.1.01886. PMID: 15817904.
22. Rasko YM, Rosen C, Ngaage LM, AlFadil S, Elegbede A, Ihenatu C, Nam AJ, Slezak S. Surgical Management of Gynecomastia: A Review of the Current Insurance Coverage Criteria. Plast Reconstr Surg. 2019 May;143(5):1361-1368. doi: 10.1097/PRS.0000000000005526. PMID: 31033818.

23. Braunstein GD. Clinical practice. Gynecomastia. N Engl J Med. 2007 Sep 20;357(12):1229-37. doi: 10.1056/NEJMcp070677. PMID: 17881754.
24. Baumgarten L, Dabaja AA. Diagnosis and Management of Gynecomastia for Urologists. Curr Urol Rep. 2018 May 17;19(7):46. doi: 10.1007/s11934-018-0796-x. PMID: 29774423.
25. Zurrida S, Nolè F, Bonanni B, Mastropasqua MG, Arnone P, Gentilini O, Latronico A. Male breast cancer. Future Oncol. 2010 Jun;6(6):985-91. doi: 10.2217/fon.10.55. PMID: 20528235.
26. Abdelwahab Yousef AJ. Male Breast Cancer: Epidemiology and Risk Factors. Semin Oncol. 2017 Aug;44(4):267-272. doi: 10.1053/j.seminoncol.2017.11.002. Epub 2017 Nov 9. PMID: 29526255.
27. Önder Ö, Azizova A, Durhan G, Elibol FD, Akpınar MG, Demirkazık F. Imaging findings and classification of the common and uncommon male breast diseases. Insights Imaging. 2020 Feb 18;11(1):27. doi: 10.1186/s13244-019-0834-3. PMID: 32072386; PMCID: PMC7028902.
28. Sansone A, Romanelli F, Sansone M, Lenzi A, Di Luigi L. Gynecomastia and hormones. Endocrine. 2017 Jan;55(1):37-44. doi: 10.1007/s12020-016-0975-9. Epub 2016 May 4. PMID: 27145756.
29. Ladizinski B, Lee KC, Nutan FN, Higgins HW 2nd, Federman DG. Gynecomastia: etiologies, clinical presentations, diagnosis, and management. South Med J. 2014 Jan;107(1):44-9. doi: 10.1097/SMJ.0000000000000033. PMID: 24389786.
30. Soliman AT, De Sanctis V, Yassin M. Management of Adolescent Gynecomastia: An Update. Acta Biomed. 2017 Aug 23;88(2):204-213. doi: 10.23750/abm.v88i2.6665. PMID: 28845839; PMCID: PMC6166145.
31. Akgül S, Kanbur N, Güçer S, Safak T, Derman O. The histopathological effects of tamoxifen in the treatment of pubertal gynecomastia. J Pediatr Endocrinol Metab. 2012;25(7-8):753-5. doi: 10.1515/jpem-2012-0105. PMID: 23155705.
32. Wibowo E, Pollock PA, Hollis N, Wassersug RJ. Tamoxifen in men: a review of adverse events. Andrology. 2016 Sep;4(5):776-88. doi: 10.1111/andr.12197. Epub 2016 May 6. PMID: 27152880.
33. Lapid O, van Wingerden JJ, Perlemuter L. Tamoxifen therapy for the management of pubertal gynecomastia: a systematic review. J Pediatr Endocrinol Metab. 2013;26(9-10):803-7. doi: 10.1515/jpem-2013-0052. PMID: 23729603.

34. Lawrence SE, Faught KA, Vethamuthu J, Lawson ML. Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynecomastia. J Pediatr. 2004 Jul;145(1):71-6. doi: 10.1016/j.jpeds.2004.03.057. PMID: 15238910.
35. Jones DJ, Holt SD, Surtees P, Davison DJ, Coptcoat MJ. A comparison of danazol and placebo in the treatment of adult idiopathic gynaecomastia: results of a prospective study in 55 patients. Ann R Coll Surg Engl. 1990 Sep;72(5):296-8. PMID: 2221763; PMCID: PMC2499206.
36. Riepe FG, Baus I, Wiest S, Krone N, Sippell WG, Partsch CJ. Treatment of pubertal gynecomastia with the specific aromatase inhibitor anastrozole. Horm Res. 2004;62(3):113-8. doi: 10.1159/000079882. Epub 2004 Jul 20. PMID: 15273427.
37. Berger O, Landau Z, Talisman R. Gynecomastia: A systematic review of pharmacological treatments. Front Pediatr. 2022 Nov 1;10:978311. doi: 10.3389/fped.2022.978311. PMID: 36389365; PMCID: PMC9663914.
38. Malhotra AK, Amed S, Bucevska M, Bush KL, Arneja JS. Do Adolescents with Gynecomastia Require Routine Evaluation by Endocrinology? Plast Reconstr Surg. 2018 Jul;142(1):9e-16e. doi: 10.1097/PRS.0000000000004465. PMID: 29952889.
39. Waltho D, Hatchell A, Thoma A. Gynecomastia Classification for Surgical Management: A Systematic Review and Novel Classification System. Plast Reconstr Surg. 2017 Mar;139(3):638e-648e. doi: 10.1097/PRS.0000000000003059. PMID: 28234829.
40. Webster JP. Mastectomy for Gynecomastia Through a Semicircular Intra-areolar Incision. Ann Surg. 1946 Sep;124(3):557-75. PMID: 17858862; PMCID: PMC1803097.
41. Hammond DC. Surgical correction of gynecomastia. Plast Reconstr Surg. 2009 Jul;124(1 Suppl):61e-68e. doi: 10.1097/PRS.0b013e3181aa2dc7. PMID: 19568140.
42. Boljanovic S, Axelsson CK, Elberg JJ. Surgical treatment of gynecomastia: liposuction combined with subcutaneous mastectomy. Scand J Surg. 2003;92(2):160-2. doi: 10.1177/145749690309200209. PMID: 12841558.
43. Kasielska A, Antoszewski B. Effect of operative treatment on psychosocial problems of men with gynaecomastia. Pol Przegl Chir. 2011 Nov;83(11):614-21. doi: 10.2478/v10035-011-0097-2. PMID: 22246094.
44. Laituri CA, Garey CL, Ostlie DJ, St Peter SD, Gittes GK, Snyder CL. Treatment of adolescent gynecomastia. J Pediatr Surg. 2010 Mar;45(3):650-4. doi: 10.1016/j.jpedsurg.2009.11.016. PMID: 20223338.