Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-026-02915-2

CONSENSUS STATEMENT

Management of gynecomastia in adolescence and adults: the clinical practice guidelines from the Italian Society of Andrology and Sexual Medicine (SIAMS)

Carlotta Pozza[1] · Riccardo Selice[2] · Arcangelo Barbonetti[3] · Valeria Hasenmajer[1] · Francesco Lotti[4,5] · Davide Menafra[6] · Daniela Pasquali[7] · Andrea Sansone[8] · Andrea M. Isidori[1,9] · Vincenzo Rochira[10,11]

Received: 11 November 2025 / Accepted: 1 May 2026
© The Author(s) 2026

Abstract

Purpose Gynecomastia, defined as thebenign proliferation of male breast glandular tissue, is a common condition in both adolescence and adulthood, often associated with physical discomfort and psychological distress. Despite its high prevalence, clinical management is frequently inconsistent and lacks standardized, evidence-based recommendations.

Methods The Italian Society of Andrology and Sexual Medicine (SIAMS) convened a multidisciplinary expert panel to develop updated clinical practice guidelines for the evaluation and management of gynecomastia. Recommendations were formulated based on a systematic review of the available literature and developed through expert consensus according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system. The document was critically reviewed and approved by the SIAMS Executive Committee.

Results The guidelines address physiological, pharmacological, pathological, congenital, and genetic forms of gynecomastia, providing a structured diagnostic and therapeutic approach. Clinical assessment, including detailed history and examination, is the cornerstone of diagnosis, and should be complemented by targeted hormonal and imaging investigations when appropriate. Observation is recommended for physiological or recent-onset cases. Pharmacological therapy may be considered in selected idiopathic or painful forms, whereas testosterone replacement should be restricted to men with proven hypogonadism. Surgery is indicated for long-standing fibrotic gynecomastia or significant psychological distress. Psychological support is also advised, especially for adolescents.

Conclusions These SIAMS Guidelines provide an evidence-based, standardized framework for the diagnosis and management of gynecomastia, promoting individualized, multidisciplinary care and identifying priorities for future research.

Keywords Gynecomastia · Male breast disorders · Testosterone · Estradiol · Prolactin · Adolescence · Adult · Hypogonadism

Methods

The Italian Society of Andrology and Sexual Medicine (SIAMS) established an expert task force to develop updated guidelines on gynecomastia aimed at providing practical guidance for the clinical evaluation and management of gynecomastia in adolescents and adults. A multidisciplinary panel of experts in andrology, endocrinology, pediatric endocrinology, and related fields was convened by SIAMS and identified the main clinical domains relevant to gynecomastia management, including pathophysiology, causes, diagnostic evaluation, laboratory assessment, imaging, and therapeutic approaches. Key clinical questions were formulated using the PICOS framework (Population, Intervention, Comparator, Outcomes, Study design) when applicable. A structured literature search was conducted primarily using the PubMed/MEDLINE database to identify relevant publications addressing the epidemiology, pathophysiology, diagnosis, and treatment of gynecomastia. The search included studies published up to June 2025, using

Extended author information available on the last page of the article

Published online: 08 June 2026

combinations of keywords such as "gynecomastia", "male breast enlargement", "etiology", "diagnosis", "hormonal evaluation", "imaging", and "treatment". Additional studies were identified through manual review of reference lists. Both observational studies and interventional studies were considered, with particular attention to diagnostic strategies, endocrine causes, drug-induced gynecomastia, and medical or surgical treatment options. When high-quality comparative evidence was not available, recommendations were based on best available evidence together with expert consensus and clinical judgement. The strength of recommendations and the certainty of the supporting evidence were classified according to the principles of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework [1], in which a strength rating 1 corresponds to a strong recommendation ("we recommend") and a rating of 2 to a weaker recommendation ("we suggest"). The quality of evidence is categorized into four levels, visually represented as follows: ØOOO for "very low-quality evidence," ØØOO for "low quality," ØØØO for "moderate quality," and ØØØØ for "high quality." Given the limited availability of high-quality comparative studies in several areas of gynecomastia management, some statements reflect expert consensus supported by the available literature and should not be interpreted as evidence-based recommendations.

Draft recommendations were developed by the writing group, coordinated by the senior author and two members of the SIAMS Guideline Committee, and subsequently discussed by the entire panel until consensus was reached. The final document was reviewed and approved by the SIAMS panel and Executive Committee and was made available to SIAMS members for two weeks on the society's website, siams.info, to collect additional feedback before submission to the Journal of Endocrinological Investigation for international peer review.

Introduction

Gynecomastia is defined as a generalized benign growth of glandular tissue in the male breast leading to palpable and/or visible swelling of breast tissue in boys or men. Gynecomastia is the most common breast disorder in men and is generally considered significant in adult men when there is palpable breast tissue [2, 3]. The etymology comes from Greek origin combining the words gyneaikaco (female woman) and mastòs (breast), probably via the French term gynécomastie or the German terms Gynäkomastie or gynecomasti. The first known use of gynecomastia was in 1881 (https://www.merriam-webster.com/dictionary/gynecomastia). Gynecomastia is a common observation in the general population [4], and can be unilateral or bilateral, most commonly the latter [5]. Gynecomastia must be distinguished from pseudogynecomastia (lipomastia), which is characterized by excessive fat deposition without glandular proliferation, by comparing the results of palpation of the subareolar fat with the adjacent subcutaneous fat in the anterior axillary fold or other areas of the chest wall [6, 7].

Physiological gynecomastia occurs in neonates, adolescents, and older men, reflecting transient hormonal changes, while pathological gynecomastia can be secondary to endocrine disorders, systemic diseases, drug-induced effects, or idiopathic causes. The clinical approach to gynecomastia is often inconsistent, with some cases receiving only a superficial assessment, while others undergo unnecessary investigations. The diagnostic process should be systematic and comprehensive, integrating a thorough medical history, a careful physical examination, and, when appropriate, biochemical and imaging studies. Beyond its medical implications, gynecomastia can significantly impact psychological well-being, affecting body image, self-esteem, and social interactions, particularly in adolescents and young adults. Several guidelines and expert opinions exist regarding the diagnostic and therapeutic approach to gynecomastia, yet no universal consensus has been established [3, 4, 6–8]. The aim of this document is to provide a structured and evidence-based approach to the evaluation and management of gynecomastia, offering recommendations that align with current clinical practice while addressing existing gaps in knowledge and patient care (Fig. 1).

Epidemiology

The prevalence of gynecomastia can vary widely (4%–69%) and is influenced by factors such as age, underlying medical conditions, medications, and lifestyle factors [4, 9–11]. Male patients complaining of gynecomastia have increased significantly in recent years [12]. According to later epidemiological data, the rate of men reporting breast soreness would seem to have risen from 0.8% to 2.4% in 20 years [13]. According to different studies, 30 to 65% of adult males have palpable breast tissue [4, 8, 11, 14, 15]. Gynecomastia can occur at any age but is most common during three distinct life stages in males: infancy, puberty, and older age.

Newborn and infancy

Some estimates suggest that temporary breast enlargement occurs in 60–90% of infants. . In infants, gynecomastia is mainly due to the influence of maternal hormones (i.e. high fetal blood levels of estradiol and progesterone) that

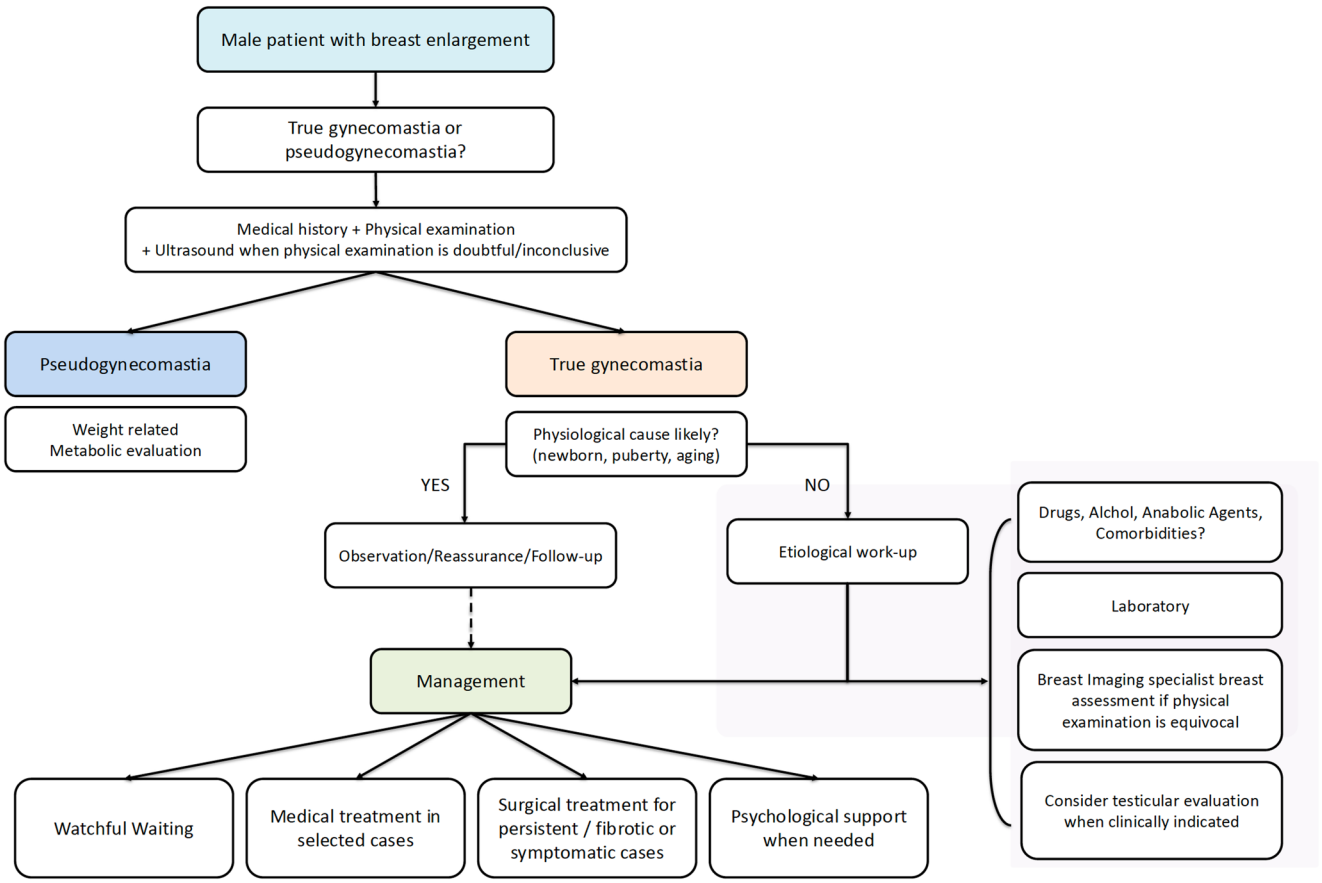


Fig. 1 Diagnostic and management algorithm for gynecomastia. Initial clinical assessment (history and physical examination, with ultrasound when needed) distinguishes true gynecomastia from pseudogynecomastia. Physiological causes are first considered; otherwise, a targeted etiological work-up is performed. Imaging and specialist evaluation are reserved for suspicious or inconclusive cases. Management is tailored to the underlying cause and clinical presentation

stimulate breast tissue in the newborn. Another mechanism is the increased conversion of steroid hormone precursors to sex steroids and increased aromatization of androgen because 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" [3, 6]. Boys also have a "mini-puberty" occurring during the first months after birth [16], with a temporary increase in adult serum gonadotropin concentrations resulting in an imbalance of estradiol to testosterone ratio with serum estradiol concentrations exceeding that of serum testosterone [4, 17], a condition that can induce gynecomastia.

Puberty

Pubertal gynecomastia is quite common and is estimated to affect up to 70% of adolescent boys [10]. It is typically a benign and self-limiting condition that usually resolves within a few years as hormone levels stabilize [9].

Aging

Gynecomastia prevalence increases with age, and it is more common in older men. In adult males, the prevalence is estimated to be around 30% to 50%, with variations based on different population studies. 57% of healthy older men [15], and more than 70% of hospitalized elderly men [8] present gynecomastia. Drug-induced gynecomastia accounts for 20% to 25% of cases [18], reaching the 80% in some studies [19]. Even with detailed evaluation, there is no identifiable cause in about 25% of cases.

Pathophysiology

Gynecomastia mainly occurs as a consequence of a change in the endocrine balance involving androgens and estrogens at the level of the breast tissue [6, 20]. Outside the context of some genetic causes with self-explanatory pathogenetic mechanism (e.g. aromatase excess syndrome [21]), the exact pathophysiological mechanisms resulting in the

development of gynecomastia have not been completely elucidated [4]. Several factors can contribute to this imbalance, from physiological or para-physiological conditions, such as puberty and aging, to more severe conditions, including hormone-secreting tumors.

From an endocrine point of view, several hormones are involved in the pathogenesis of gynecomastia [22], among which the most important are estrogens and androgens. Activation of the estrogen receptor acts as a proliferative signal for breast tissue, whereas activation of the androgen receptor results in inhibitory effects on tissue growth. The delicate balance between these two antagonist systems influences the growth of breast tissues during development, possibly providing a rationale to transient, benign forms of gynecomastia occurring during puberty and with aging. Both conditions of decreased androgen activity and estrogen excess can thus be involved in the pathogenesis of gynecomastia. Gonadotropins also play an important role in the hormonal regulation underlying gynecomastia. Luteinizing hormone (LH) stimulates testicular Leydig cells to produce testosterone, while follicle-stimulating hormone (FSH) is involved in testicular function and spermatogenesis. Alterations in gonadotropin secretion may therefore contribute to conditions of androgen deficiency or imbalance between androgen and estrogen action. In primary hypogonadism, increased LH and FSH levels reflect impaired testicular testosterone production, which may favor the development of gynecomastia through reduced androgenic inhibition of breast tissue growth. Conversely, in secondary hypogonadism, reduced gonadotropin secretion results in decreased testosterone production with similar downstream effects. In addition, human chorionic gonadotropin (hCG) can stimulate Leydig cells and increase testicular estrogen production. Pathological elevations of hCG, such as those occurring in certain germ cell tumors or other hCG-secreting neoplasms, may therefore contribute to the development of gynecomastia through increased estrogenic stimulation. It is important to note, however, that gynecomastia might occur in conditions in which the ratio between estrogen and androgen activity is affected, despite no overt endocrine derangement [4, 23]. Several forms of male hypogonadism feature gynecomastia in association with a decrease in testosterone levels [24], with or without reaching overtly pathological levels, such as in the case of Klinefelter Syndrome [25–27]. Likewise, forms of impaired receptor activity, such as in partial androgen insensitivity syndromes [28, 29] or in individuals with higher number of CAG repeats in the gene encoding the androgen receptor [30], can result in the development of gynecomastia. Other environmental factors, such as obesity, alcohol use, use of appearance and performance enhancing drugs, recreational drug use, several medications, and malnutrition are also affecting the balance between androgens and estrogens [7]. In the newborn, transplacental maternal estrogens and progesterone transfer can stimulate breast tissue development, jointly with increased conversion of steroid hormone precursors to sex steroids and increased aromatization of androgen because of neonatal surge of luteinizing hormone (LH). Indeed, neonatal gynecomastia may persist for several weeks after birth [3, 22, 31–33], beyond maternal hormones withdrawal [4] and moreover gestational age at birth seems to affect the size of neonatal breast tissue [34]. Additionally, other hormones might be involved in the pathogenesis of gynecomastia, such as prolactin, IGF-1 and progesterone, whose receptors are present and coexpressed in breast tissue [35–37]. Hyperprolactinemia can exert suppressive effects on the hypothalamus-pituitary-gonadal axis and a direct effect on epithelial cell proliferation has also been postulated: however, the suppressive effects on the axis might decrease estrogen action, thus limiting the potential risk of developing gynecomastia [38].

Causes of gynecomastia

Physiological

Recommendations

R1. *We suggest avoiding starting an extensive diagnostic work-up before ruling out physiological causes of gynecomastia, as unnecessary investigations may lead to overmedicalization and overdiagnosis (Expert opinion).*

Evidence

Breast development in males can occur normally during three phases of life, neonatal, puberty and aging. Physiologic gynecomastia is usually transient, bilateral, smooth, firm and symmetrically distributed under the areola. Most of the enlargement is due to proliferation of stroma and not of breast ducts.

Newborn and infants: Palpable breast tissue can be observed overtly or palpably in newborn as a consequence of transplacental exposure to maternal estrogens [31] and gestational age at birth seems to affect the size of neonatal breast tissue [34]. Some studies have reported breast tissue to be more frequent and pronounced in girls than in boys [39], independently from body weight, while others did not observe gender difference in the occurrence or size of breast tissue [34]. Neonatal breast enlargement is usually transient and commonly regresses spontaneously within the first weeks after birth as maternal hormone levels decline. However, palpable breast tissue may persist for several months in otherwise healthy infants (Add REF 17 PMID 20493740)

and, in isolation, does not necessarily indicate an underlying pathological condition. Further evaluation should therefore be reserved for cases characterized by progressive enlargement, asymmetry, signs of inflammation, or the presence of additional clinical findings suggesting an endocrine or systemic disorder.

Puberty One-half of adolescent males will experience gynecomastia, with a peak incidence between 13 and 14 years of age or pubertal stages G3 and G4. Pubertal estrogen production begins prior to testosterone production due to early maturation of aromatase, and the increase of estrogen to testosterone ratio could promote glandular proliferation. In addition, other mediators, as GH and IGF-1, can sustain breast development [40]. During puberty, the interplay between sex steroids and the somatotropic axis is critical. GH and IGF-1, through their effects on GnRH neurons and gonadotropin secretion, promote pubertal development and indirectly influence breast tissue proliferation. Locally, IGF-1 enhances steroidogenesis and may amplify estrogen activity, while estradiol modulates GH secretion and suppresses IGF-1 production. This hormonal dynamic fosters a balance essential for normal pubertal progression and contributes to the transient nature of pubertal gynecomastia [41]. Recent studies have shown a significant positive association between breast enlargement and IGF-1 levels during puberty, namely boys who developed gynecomastia reached an age at peak height velocity earlier compared to boys who did not develop gynecomastia [42, 43]. Regression spontaneously occurs in 75–90% adolescents within 6 months to 1–2 years in most cases [44], when the ratio is restored [22, 45]. This means that in case of primary pubertal gynecomastia the correct conduct is observation and reassurance without specific treatment [44]. However, in a subset of adolescents, gynecomastia may persist beyond the typical period of spontaneous resolution, causing significant physical or psychological discomfort [46]. Persistent gynecomastia is often associated with sustained hormonal imbalances, obesity, or other underlying conditions [7]. In these cases, where gynecomastia remains stable or progresses, therapeutic intervention may be warranted to alleviate symptoms and improve quality of life.

Aging Up to 65% of men may develop gynecomastia during aging, largely as a consequence of changes in the balance between androgenic and estrogenic activity [22]. With advancing age, circulating testosterone levels tend to decline, while several factors, including increased adiposity and enhanced peripheral aromatase activity may contribute to relatively greater estrogenic influence at the breast tissue level. In many cases, this imbalance reflects not necessarily an absolute increase in circulating estradiol, but rather a relative shift in the estrogen-to-androgen activity ratio.

Age-related hormonal changes may further modify this balance. Serum sex hormone binding globulin (SHBG) concentrations increase with age which reduces the fraction of bioavailable testosterone to a greater extent than that of estradiol due to the higher binding affinity of SHBG for androgens. As a consequence, the bioavailable estradiol-to-testosterone ratio may increase, favoring estrogenic effects at the breast tissue level [45, 47]. However, while gynecomastia in adults is frequently attributed to physiological aging or medications, these apparent causes should not preclude a thorough investigation to exclude underlying pathological condition.

Remarks

Gynecomastia during neonatal, pubertal, and aging phases is typically physiological and self-limiting condition in most cases, requiring only observation and reassurance. Understanding the transient nature of these changes helps avoid unnecessary interventions. Persistent gynecomastia beyond the expected timeframe warrants careful evaluation. Psychological distress associated with gynecomastia can significantly impact quality of life, self-esteem, and social interactions and underscores the need for a holistic approach to management, addressing both physical and emotional aspects. Differentiating physiological gynecomastia from pathological causes is essential across all life stages. Clinical history, hormonal evaluation, and consideration of patient age provide critical context for determining when intervention is necessary.

Drug Induced

Recommendations

R1 *We recommend carefully reviewing the patient's medication history in order to identify drugs potentially associated with gynecomastia (1 ØØØO).*

Evidence

Drug-related gynecomastia is one of the most common forms of adult-onset gynecomastia, since gynecomastia could be caused by drugs in 10–25% of cases [3, 6, 15, 48]. Several drugs have been associated with the risk of gynecomastia occurrence, and the most relevant drug classes and proposed mechanisms are summarized in Table 1.

Drugs having direct hormonal activity have been widely associated with the occurrence of gynecomastia, since they

Table 1 Medications associated with gynecomastia and their mechanisms. Medications associated with gynecomastia and the proposed endocrine mechanisms of action/disruption

Category	Drug	Mechanism of action
Drugs with direct hormonal activity	Exogenous estrogens, estrogenic creams, anabolic steroids, hCG, GH	Disrupt estrogen-androgen balance, direct estrogenic stimulation
Drugs with estrogenic activity	Phytoestrogens (soy products, plant-based estrogens), Digitalis glycosides	Estrogen receptor activation, inhibition of testosterone synthesis
Anti-androgens	Flutamide, Bicalutamide, Enzalutamide, Spironolactone, Cyproterone acetate	Androgen receptor blockade, increased estrogen effects
5-Alpha reductase inhibitors	Finasteride, Dutasteride	Inhibition of DHT synthesis, increased estrogen-to-androgen ratio
GnRH agonists	Leuprolide, Goserelin	Suppression of gonadal testosterone production
Ketoconazole	Ketoconazole	Inhibition of steroidogenesis, suppression of testosterone synthesis
Proton pump inhibitors	Omeprazole, Esomeprazole	Inhibition of estradiol catabolism via CYP3A4
Gastrointestinal drugs	Cimetidine, Ranitidine	Weak androgen receptor blockade
Cardiovascular drugs	Calcium Channel Blockers (Diltiazem, Verapamil, Nifedipine), Digoxin, Amiodarone	Secondary hypogonadism, unclear mechanisms
Psychotropic drugs	Diazepam, Haloperidol, Phenothiazines, Tricyclic Antidepressants	Elevated prolactin levels leading to secondary hypogonadism
Chemotherapeutic agents	Alkylating Agents, Vincristine, Methotrexate	Suppression of testosterone, increased LH, estrogenic effects
Drugs of abuse	Alcohol, Marijuana, Heroin, Methadone	Estrogenic activity, suppression of testosterone synthesis
Antiretroviral therapy (HAART)	Various HIV treatment drugs	Direct mammotrope effects, prolactin elevation
Statins	Atorvastatin, Simvastatin	Decreased cholesterol synthesis leading to reduced testosterone production
Miscellanea	Phenytoin, Amphetamines, Domperidone, Metoclopramide, Isoniazid, ACE inhibitors, Nitrates, Isoniazid, Metronidazole	Uncertain mechanisms

hCG = human chorionic gonadotropin; GH = growth hormone; DHT = dihydrotestosterone; LH = luteinizing hormone; HAART = highly active antiretroviral therapy; ACE = angiotensin-converting enzyme

could contribute to the imbalance of the estrogen to androgen ratio, therefore inducing breast gland enlargement [3, 22, 48].

Compounds having stimulating activity on estrogen receptors have been demonstrated to cause gynecomastia and include: exogenous estrogens used for the treatment of prostate cancer, estrogenic creams used to treat baldness, foods derived by animals treated with estrogenic hormonal stimulation or supplementary foods containing phytoestrogens, manufacture-derived exposure to estrogen-containing drugs, abuse of substance like marijuana which plant has been suggested to contain estrogens, and cardiac agents such as digitalis glycosides having structural similarities with phytoestrogens. Furthermore, for other drugs which have been related to the appearance of gynecomastia with an unclear pathophysiological mechanism, a possible estrogen-related activity has been hypothesized: for example, for antitumoral chemotherapeutic drugs such as alkylating agents, it has been assumed that gynecomastia could be induced by a relative estrogenic excess deriving from increased levels of LH which could on one hand compensate for testosterone deficiency creating a picture of subclinical hypogonadism, on the other hand stimulate increased estrogen production, while for proton pump inhibitors (PPIs) such as omeprazole and esomeprazole currently used for the medical treatment of peptic ulcer, it has been hypothesized that gynecomastia could be caused by an estrogenic excess derived from the inhibition of estradiol catabolism by cytochrome P450 (CYP) 3A4 [48–50]. Drugs acting with anti-androgenic effects have also been frequently associated with the occurrence of gynecomastia: in particular, they include androgen receptor antagonists and GnRH agonists used for the treatment of prostate cancer, 5-alfa reductase inhibitors acting through the reduction of DHT levels such as finasteride and dutasteride used for the symptomatic treatment of prostate hyperplasia, and ketoconazole (used as antifungal and adrenostatic therapy) acting through steroidogenesis and inhibition of testosterone synthesis.

Furthermore, spironolactone, an aldosterone receptor antagonist currently used for the treatment of heart failure and arterial hypertension, has been frequently associated with the occurrence of gynecomastia through multiple antiandrogenic mechanisms. In particular, spironolactone may inhibit testosterone synthesis, antagonize the androgen receptor, and interfere with androgen metabolism thereby reducing androgenic activity and promoting a relative

imbalance between androgenic and estrogenic effects at the breast tissue level [6, 48, 51].

In addition, hormonal therapies used both for the treatment of endocrinological disorders and to increase sport performance have been frequently associated with gynecomastia and are considered the most common cause of gynecomastia when used as doping substances, including androgens and anabolic agents that could be aromatized into estrogens, human chorionic gonadotropin and growth hormone [22].

Lastly, other drugs have been associated to gynecomastia with uncertain pathophysiological mechanisms; for some of these, including cardiac agents such as calcium-channel blockers, anti-ulcer drugs like anti-histamine receptor 2 cimetidine and neuroleptics with dopamine-receptor antagonist activity it has been hypothesized that gynecomastia could be caused by secondary hypogonadism induced by iatrogenic hyperprolactinemia, whereas for antiretroviral therapies used for HIV treatment a direct mammotrope effect and for statins used for treatment of hypercholesterolemia a reduction of testosterone secondary to decreased cholesterol synthesis have been supposed [6, 15, 22, 48].

Remarks

Drug-induced gynecomastia represents one of the most common causes of adult-onset gynecomastia. Several classes of drugs have been implicated, primarily through mechanisms that disrupt the estrogen-to-androgen ratio. Medications with direct hormonal activity, such as exogenous estrogens, anabolic steroids, and certain anti-androgenic therapies, can promote glandular breast enlargement. Drugs with estrogenic effects, including digitalis glycosides, phytoestrogen-containing supplements, and some chemotherapeutic agents, may induce gynecomastia via direct receptor stimulation or secondary hormonal imbalances. Anti-androgenic drugs, such as androgen receptor antagonists, GnRH agonists, 5-alpha reductase inhibitors, and spironolactone, are commonly associated with gynecomastia due to their interference with androgen synthesis and action. Additionally, some medications with unclear pathophysiological mechanisms, including PPIs, calcium-channel blockers, H2-receptor antagonists, neuroleptics, antiretroviral therapies, and statins, have been linked to gynecomastia, possibly through effects on hormone metabolism or secondary hypogonadism. Given the wide range of implicated drugs, a careful medication history is essential when evaluating patients with gynecomastia to identify potential iatrogenic causes and guide appropriate management.

Pathological: endocrine diseases/other

R1 *We recommend ruling out possible pathological causes of gynecomastia secondary to different hormonal and non-hormonal diseases based on patient's clinical history, physical examination and tailored diagnostic work-up (1 ØØØO).*

R2 *After excluding organic, drug- or hormonal-induced gynecomastia, we suggest thorough clinical history evaluation and patient consultation for behavioral causes of gynecomastia, with specific attention to recreational drugs and alcohol use (Expert Opinion).*

Endocrine (hormonal) causes of gynecomastia

Evidence Hormones are the main regulators of breast enlargement in both males and females, and endocrine conditions are among the most common causes for pathologic gynecomastia. Any endocrine disorder altering the estradiol/testosterone ratio activity in the breast can induce gynecomastia in otherwise healthy adult males, even though other hormones seem to play a role in pathologic conditions. Aside from iatrogenic causes of increased estradiol or decreased testosterone such as treatment with anabolic steroids or unintentional exposure to estrogens, endocrine causes of gynecomastia can be therefore divided into (I) conditions causing absolute or relative reduction in testosterone levels, (II) conditions characterized by increased estrogen synthesis. The latter can be associated to low or high levels of testosterone.

Testosterone and estradiol Primary and secondary hypogonadism are both characterized by low testosterone levels, resulting in a decrease of the inhibitory effect of androgens on the growth and differentiation of the breast tissue, and an increased estrogen to testosterone ratio. Causes of primary and secondary hypogonadism are too numerous to count in this manuscript but are available within guidelines on male hypogonadism [24]. Estrogen activity is also influenced by aromatase-mediated conversion of androgen precursors [15]. In hypogonadal men, adrenal production of steroid precursors may remain relatively preserved despite reduced testicular testosterone secretion. This condition may contribute to a relative imbalance between estrogenic and androgenic activity rather than reflecting a consistend absolute increase in circulating estradiol levels.

In primary hypogonadism testicular failure causes an increase in LH secretion, which also enhances the activity of aromatase [52].

Klinefelter syndrome (KS) is the most common cause of primary hypogonadism, characterized by early testicular

failure, increased LH levels and testicular degeneration [53, 54]. Patients with KS often experience gynecomastia both due to low circulating testosterone and increased aromatase activity [25].

In secondary hypogonadism, low testosterone is associated with low or inappropriately normal levels of gonadotropins, that can be either due to hypothalamic/pituitary organic failure or to functional conditions such as aging, concomitant illnesses and obesity [55–58]. In obese patients, increased aromatase activity has also been described [59].

In some cases, gynecomastia may serve as an early indicator of hormone-secreting tumors, which can include Leydig cell tumors (LCTs), Sertoli cell tumors, granulosa cell tumors, gonadal and extra-gonadal germ cell tumors [60]. Such neoplasms can disrupt the balance between androgens and estrogens, leading to clinical manifestations that range from gynecomastia to infertility. Leydig cell tumors can synthesize androgens, estrogens or both, depending on their functional status, however while gynecomastia is often cited as a frequent clinical presentation of LCTs [61], some authors found it to be less prevalent, suggesting that gynecomastia might not always be a prominent feature in all populations with LCTs [62]. Germ-cell tumors may produce beta-human chorionic gonadotropin, which can stimulate estrogen synthesis, thus suppressing gonadotropins and exacerbating the estrogen-androgen imbalance with consequent clinically manifest gynecomastia [63]. It is reported that 5–7% of GCT present with gynecomastia with an equal incidence between seminomas and non-seminomatous germ cell tumors [64]. The early recognition of gynecomastia as a paraneoplastic phenomenon can significantly impact clinical outcomes .

Other endocrine conditions characterized by the development of gynecomastia are thyroid disorders, GH/IGF-1 excess or defect and hyperprolactinemia.

Thyroid hormones Thyroid dysfunction leads to gynecomastia mostly disrupting the hypothalamic- pituitary-gonadal axis [65] and breast enlargement can be present as a concomitant – and even first [66] – symptom in both hyperthyroid and hypothyroid patients. In longstanding severe hypothyroidism, prolactin levels are significantly increased due to high TRH levels, thus leading to hypogonadism. On the other hand, men with hyperthyroidism show increased levels of SHBG and consequent relative hypogonadism, which in turn increase LH secretion and aromatization of androgens to estrogens, possibly promoting the development of gynecomastia.

GH and IGF-1 GH and IGF-1 are key mediators of estrogen and progesterone activity, and estrogens induce expression of IGF-1 receptors on breast tissue. The stimulatory effect of IGF-1 on breast formation may be synergized by estradiol [42].

Gynecomastia has been described in acromegaly patients [67], and as side effect of GH treatment. Studies on correlation with IGF-1 values in patients with gynecomastia have yielded conflicting results [42, 68]. As for prolactinomas, GH-secreting pituitary adenomas can also cause gynecomastia by inducing hypogonadism for compression or pituitary stalk damage.

Prolactin The mechanisms of hyperprolactinemia-induced gynecomastia are still under debate.

Hyperprolactinemia does not appear to directly stimulate breast gland proliferation in males. Rather, elevated prolactin levels may suppress the hypothalamic–pituitary–gonadal axis, leading to secondary hypogonadotropic hypogonadism and reduced testosterone secretion. The resulting decrease in androgenic inhibition of breast tissue may favor the development of gynecomastia.

Prolactin and progesterone receptors have been identified in male breast tissue [22, 35], suggesting that prolactin might have a modulatory role in breast physiology [69]. However, current evidence indicates that hyperprolactinemia contributes to gynecomastia primarily through its effects on gonadal function rather than through a direct mammotropic effect [70].

Remarks

The recommendation to exclude pathological entities associated with gynecomastia in adults, even in the presence of an apparent modifiable cause, places a high value on detecting life-threatening organic causes. In clinical practice, the diagnostic evaluation should follow a pragmatic prioritization based on prevalence and clinical relevance. Physiological conditions (puberty, aging and obesity) and drug- or substance-related causes should be considered first, followed by hypogonadism or endocrine disorders, chronic liver or kidney disease, and finally rare causes such as hormone-secreting tumors. The diagnosis of an organic cause of gynecomastia imposes to reevaluate gynecomastia after the removal of or the effective treatment of the primary disorders, leaving medical or surgical treatment of gynecomastia only in case of persistent breast enlargement.

Other causes

Evidence Aside from endocrine disorders, several other conditions have been associated with the development of gynecomastia. For most, underlying causes are ultimately

an imbalance in testosterone and estrogen levels, including reduced testosterone bioavailability.

Kidney disease In patients with chronic kidney disease (CKD), gynecomastia is often reported as an adverse drug-related event [71]. However, both hypogonadism and hyperprolactinemia have been reported in men with chronic kidney disease (CKD) as well [72], further contributing to the development of breast tissue.

Liver disease Gynecomastia has been described in patients with liver conditions, including HCV infection and cirrhosis [73]. Male patients with liver insufficiency often develop hypogonadism [74]. Reduced free testosterone availability and increased estrogen levels due to altered liver metabolism and SHBG synthesis are characteristic of cirrhosis and other liver conditions [75]. Actually, increased SHBG conditions are often characterized by altered T/E ratio, since SHBG binds testosterone more avidly than estrogen. Among the clinical consequences, increase in breast tissue has been described, and a recent epidemiological study has identified a fivefold risk for death to hepatic failure in patients with gynecomastia [76]. It is worth mentioning that several cirrhosis patients have an associated history of alcohol abuse, which is an independent factor contributing to the development of gynecomastia.

HIV infection and treatment In men living with HIV, earlier reports identified a significantly increased prevalence of gynecomastia, both before starting highly active antiretroviral therapy (HAART) and, more frequently, afterwards [77, 78], with an estimated prevalence around 2.8–2.9% [79, 80]. The occurrence of unilateral or bilateral gynecomastia in men living with HIV was associated to many pathological mechanisms. First, the concomitant presence of HCV-induced cirrhosis, alcohol and recreational drug use, along with treatment for other conditions such as neurological complications are non-HIV-related predisposing mechanisms [79]. Second, there is an increased prevalence of hypogonadism in men living with HIV that could alter the estrogen/testosterone ratio leading to breast tissue enlargement [81]. Among HAART-related proposed mechanisms is included the occurrence of lipodystrophy (peripheral fat tissue wasting), immune reconstitution and mitochondrial toxicity, and estrogen receptor modulation [82]. The relative importance of each one in the development and natural history of breast enlargement is still unclear. An association with protease inhibitors and efavirenz has been highlighted by cohort studies [77, 79, 83] but similar symptoms have been reported under other regimens as well [84]. Malignant breast cancer was described anecdotally in men with HIV developing gynecomastia, suggesting a cautious and thorough evaluation at diagnosis [85, 86]. Proposed treatments for benign enlargement included local DHT injections [87] and tamoxifene [88]. However, many cases also showed a spontaneous resolution.

Alcohol An association between alcohol abuse and gynecomastia has been confirmed by recent population studies [89], reporting alcohol abuse as the second more prevalent risk factor, after medication, for gynecomastia in a Danish nationwide register cohort. Aside from alcoholic cirrhosis and liver disease, an independent effect of alcohol on SHBG [90] and Leydig cells [91] has been proposed.

Recreational drugs Use of cannabis has been associated with gynecomastia. A few mechanisms, such as increased prolactin or decreased available testosterone, have been proposed [92]. Even if a recent study suggests an association [93], the exact physiological mechanism is still under debate [94].

Remarks

Disease- or behavioral-associated causes for gynecomastia should be investigated to identify modifiable factors only after potential life-threatening conditions, such as hormone-secreting neoplasms, have been excluded. Modern regimens of HAART in people living with HIV are less associated with lipodystrophy and gynecomastia, but a careful and thorough evaluation and potential discussion with the infectious disease specialist is recommended after exclusion of HIV-associated hormonal imbalances.

Congenital and genetic causes of gynecomastia

R1. *We recommend ruling out genetic causes in prepubertal gynecomastia (1 ØØØO).*

R2. *We suggest ruling out genetic causes in severe peripubertal gynecomastia (2 ØØØO).*

Evidence

Pre -and peri-pubertal onset of gynecomastia may be due to genetic causes [7]. Estrogen excess due to aromatase excess syndrome is a monogenic, rare disease caused by gain-of-function mutations of the aromatase (CYP19A1) gene [21]. At present, around 30 cases have been described worldwide. Gynecomastia may occur during infancy around 5 to 7 years of age in these patients [95]. The hormonal analysis shows elevated serum estrogens (both estradiol and estrone), normal serum androstenedione, and prepubertal levels of serum total testosterone. Estrogen production derives from adrenal androgens (i.e. androstenedione) after aromatase conversion

into estrogens. Beyond gynecomastia, these patients have accelerated growth and early onset of growth spurt possibly affecting final adult height. When gynecomastia occurs in the peripubertal period usually it is of mild degree [96].

Other genetic causes of prepubertal or peri-pubertal gynecomastia are (i) partial androgen resistance [97], including also androgen insensitivity linked to CAG repeat length such as Kennedy's disease (spinal and bulbar muscular atrophy) [98], where the increased circulating testosterone favors its conversion to estradiol, (ii) Peutz-Jeghers Syndrome [99] and (iii) Carney complex [100] which are both due to increased aromatase activity and expression. Peutz-Jeghers Syndrome is characterized by gastrointestinal hamartomatous polyps and dark spots of the skin and mucous membranes (particularly around the mouth) [101] while Carney complex by myxomas, various endocrine cancers, and blue nevi [102]. Also, 11β-Hydroxylase and non-classical 21-hydroxylase deficiency may cause pre- or peri-pubertal gynecomastia in boys due to high serum levels of 17-OH progesterone and an imbalance between androgen and estrogens [103–105]. In this case, biochemical analysis is characterized by increased adrenal androgens that may be coupled with cortisol insufficiency [103–105].

Other genetic diseases leading to congenital hypogonadism may present with gynecomastia [7]. Among them congenital hypogonadotropic hypogonadism [106] and defects in steroid biosynthesis, such as P450 oxidoreductase deficiency, 17-hydroxylase/17,20-lyase and 3βHSD deficiency [7].

Ovotestis is a very rare congenital disorder of sexual development that may present with gynecomastia in the peripubertal period but is generally coupled with other anomalies of sexual development [107].

Remarks

The genetic diagnosis of aromatase excess syndrome should be guided by clinical and biochemical examinations and is based on CYP19A1 gene sequencing [21, 96, 108].

When congenital adrenal hyperplasia and defects of steroid biosynthesis are suspected, the genetic analysis should be oriented by the hormonal pattern found at biochemical analysis in order to select the candidate gene to be sequenced. Similarly, the suspicion of congenital hypogonadotropic hypogonadism and of defects of steroid biosynthesis requires confirming genetic analysis.

The clinical suspicion of ovotestis requires a more complex approach based on a multidisciplinary evaluation [109].

Evaluation

Clinical history and physical examination

Recommendations

R1. *We recommend taking an accurate and thorough medical history of any patient complaining of gynecomastia, including comorbid conditions, concomitant medications, dietary habits, and changes in sexual functioning (1 ØØØØ).*

R2. *We recommend performing a structured clinical examination followed by palpation of breast region to discriminate a diagnosis of gynecomastia or pseudogynecomastia including genital examination (1 ØØØØ).*

R3. *We recommend distinguishing through clinical examination between unilateral and bilateral gynecomastia and to exclude eventual clinical signs of suspicious malignancy in unilateral forms (1 ØØØØ).*

Evidence

The diagnostic work-up of gynecomastia begins with a thorough clinical evaluation, which includes an accurate medical history and a complete physical examination.

Medical history might provide some important clues on its pathogenesis. The onset of gynecomastia, including its suddenness and the exact timing (e.g. in association with puberty onset), is the first item to investigate when collecting medical history. Likewise, several other factors should be investigated, such as the use of medications, recreational drugs, and doping agents [15]. Nutritional status should also be investigated by enquiring on dietary regimens, also paying attention to products containing high dosages of phytoestrogens [110, 111]. Sexual history should also be collected, as a sudden loss of sexual desire, the onset of erectile dysfunction and the reduced frequency of morning erections might be suggestive of hypogonadism [24, 112]. Likewise, clinicians should look for telltale signs of other metabolic derangements associated with gynecomastia, such as edema suggestive of chronic kidney disease or liver failure, or goiter and bulging eyes suggestive of hyperthyroidism [7]. A psychological assessment is also recommended, as gynecomastia may have relevant psychological and psychosocial consequences [113]. A guideline-driven clinical examination should be performed, starting with the palpation of the breast region to distinguish true gynecomastia from pseudogynecomastia, the latter being characterized by increased subareolar fat without glandular enlargement. In this context, a crucial diagnostic role should be attributed to breast physical examination to assess the symmetry, firmness and tenderness of the subareolar tissue, which often

allows clinicians to distinguish true gynecomastia from pseudogynecomastia. [4, 6, 51]. Evidence suggests that the reliability of physical examination also depends on how it is performed: in particular, the patient should lie flat on his back with his hands clasped beneath his head in order to facilitate the examination of the axillary region and the examiner should slowly squeeze the breast between the thumb and forefinger in order to assess the gland outer limits and size. In patients with true gynecomastia, a soft, elastic or tender or firm mass of tissue that is concentric with the nipple–areolar complex is palpable, whereas in patients with pseudogynecomastia, no such disk of tissue is demonstrable [6].

Gynecomastia generally features bilateral, painless and relatively firm glandular tissue located under the nipple. Gently squeezing the subareolar tissue to assess the presence of galactorrhea (discharge of milky liquid from the nipple) may also be performed during breast examination. Since gynecomastia can present as either unilateral or bilateral [4, 114, 115], with bilateral forms being slightly more common, a careful and symmetrical breast examination is necessary to differentiate the two. In unilateral cases, special attention must be given to signs of malignancy, including a hard, tender mass located beyond the areolar limits, as well as skin changes such as ulceration, nipple retraction, or bleeding [3, 6]. On top of breast evaluation, physical examination should be performed to assess signs of virilization; genital assessment and tumor marker evaluation should be performed to exclude testicular cancer, particularly in patients presenting with unexplained gynecomastia [112, 116, 117].

Remarks

A structured diagnostic approach to gynecomastia is essential to differentiate physiological from pathological cases. A detailed medical history should be collected to investigate the onset, progression, and potential contributing factors, including medications, recreational drugs, anabolic steroids, dietary phytoestrogens, and metabolic disorders. Particular attention should be given to sexual dysfunction, which may indicate underlying hypogonadism, and systemic signs suggestive of renal, hepatic, or thyroid dysfunction. A guideline-based physical examination remains the cornerstone of diagnosis, beginning with breast palpation to distinguish true gynecomastia from pseudogynecomastia, and including genital assessment. Evaluation for galactorrhea may also be performed, as it can occasionally suggest hyperprolactinemia or pituitary disease. However, the clinical evaluation of suspected hypogonadism should follow established diagnostic guidelines, as the manifestations of hypogonadism extend beyond those associated with hyperprolactinemia alone. The distinction between unilateral and bilateral forms is crucial, as unilateral gynecomastia requires careful assessment for malignancy, with attention to hard, irregular masses, nipple retraction, ulceration, or skin changes. Psychological assessment is recommended, as gynecomastia can significantly affect self-esteem and social well-being.

Laboratory

Recommendations

R1 *We suggest evaluating LH, total testosterone, SHBG, albumin, PRL levels and β-HCG as the first diagnostic step. Measurement of estradiol may also be considered as part of the endocrine assessment, although its interpretation should be cautious due to analytical limitations and the lack of validated diagnostic thresholds. (Expert Opinion).*

R2 *We suggest including thyroid hormones, IGF-1, liver and kidney function evaluation along with any additional examination guided by patient history and clinical presentation (Expert Opinion).*

Evidence

Since an endocrine dysregulation or imbalance is supposed to be the main determining factor for gynecomastia, it is unsurprising that laboratory assessment might be a necessity. However, some Authors suggest that accurate medical history might spare the need for laboratory assessment [7] if patients have no remarkable findings, such as occurring in pubertal or late-onset gynecomastia.

If the clinical scenario deserves further investigation, a first-line approach would inevitably require an assessment of endocrine status (Table 2). Testosterone measurement should be done in the morning, after an overnight fast. As gynecomastia is a common symptom associated with hypogonadism, it is also recommended to measure SHBG and albumin levels to calculate free and bioavailable testosterone using the Vermeulen formula [118] (Table 2). Estradiol measurement may provide additional information in selected cases, particularly when clinical suspicion of estrogen excess or hormone-secreting tumors exists. However, clinicians should interpret estradiol levels with caution, as commonly used immunoassays have limited accuracy at the low concentrations typically observed in men [119–123]. When available, more reliable analytical techniques such as liquid chromatography–mass spectrometry (LC/MS) should be preferred [121] (Table 2). As already stated, clinicians should also consider that while T and E2 levels might be in the reference ranges, their ratio might be imbalanced [95].

On top of T and E2, diagnostic assessment should include measurement of LH and FSH, prolactin, TSH, GH and

Table 2 Laboratory analysis in gynecomastia. Laboratory evaluation in gynecomastia: core first-line panel and targeted second-line tests based on clinical suspicion

Parameter	Diagnostic Indication	Associated Conditions
First-line tests (recommended)		
LH	Differentiate between primary, secondary, and functional hypogonadism; Detect anabolic steroid use	Primary hypogonadism, Klinefelter syndrome, Steroid abuse, central hypogonadism
Testosterone	Assess androgen status (morning sample, fasting)	Hypogonadism
Estradiol	Evaluate estrogen excess or imbalance	Testicular tumors, aromatase excess, obesity, AIS, exogenous estrogens
SHBG	Needed to calculate free/bioavailable testosterone	Thyroid dysfunction (↑ SHBG in hyperthyroidism, ↓ in hypothyroidism)
Albumin	Needed to calculate free/bioavailable testosterone	Liver and kidney dysfunction
Prolactin	Rule out hyperprolactinemia	Prolactinoma, pituitary adenoma
β-hCG, α-FP	Tumor marker	Testicular tumors (seminomas, non-seminomas)
Suggested examination according to clinical suspicion		
TSH, fT3, fT4	To assess thyroid function	Hyperthyroidism, hypothyroidism
IGF-1	Role in pubertal gynecomastia	Acromegaly, growth disorders
Liver function evaluation	Assess hepatic contribution to hormonal imbalance	Cirrhosis, liver failure, alcohol-related liver disease, viral diseases/infections
Kidney function tests	Evaluate for renal causes of hormonal imbalance	Chronic kidney disease, hyperprolactinemia
17-OH Progesterone	To exclude congenital adrenal hyperplasia	Adrenal enzyme deficiencies, adrenogenital syndrome
Androstenedione	Precursor of estrogens via aromatization, leading to an imbalance in the estrogen/androgen ratio.	

Note: Always interpret estradiol using high-specificity assays (e.g., LC-MS/MS) when available; The T: E2 ratio may be more relevant than absolute values in some cases. The choice of second-line tests should be guided by clinical presentation

LH = luteinizing hormone; SHBG = sex hormone–binding globulin; β-hCG = beta–human chorionic gonadotropin; α-FP = alpha-fetoprotein; TSH = thyroid-stimulating hormone; fT3 = free triiodothyronine; fT4 = free thyroxine; IGF-1 = insulin-like growth factor 1; 17-OH progesterone = 17-hydroxyprogesterone; AIS = Androgen Insensitivity Syndrome

IGF-1 and, based on clinical suspicion, biomarkers of testicular cancer (including α-fetoprotein and hCG) (Table 2). In case of suspicion of hypogonadism clinical examinations should be performed according to guidelines for the management of male hypogonadism [24]. Specifically, gonadotropin levels can guide the clinician towards other conditions affecting the endocrine balance between androgens and estrogens: increased LH levels, being a marker of impaired testicular response, suggest a diagnosis of subclinical hypogonadism [112, 124], whereas high T levels associated with suppressed FSH and LH could be suggestive of use of androgen anabolic steroids [22] or of endogenous testosterone secretion stimulated by betaHCG, as occurring in testicular tumors [63, 125–127]. Thyroid function is usually assessed by measurement of TSH levels, although it might be useful to also consider dosing thyroid hormones (fT3, fT4) in selected cases. GH and IGF-1 can sustain breast development [40]; this is of paramount importance in puberty, when the interplay between sex steroids and the somatotropic axis is critical. GH and IGF-1, through their effects on GnRH neurons and gonadotropin secretion, promote pubertal development and indirectly influence breast tissue proliferation. Locally, IGF-1 enhances steroidogenesis and may amplify estrogen activity, while estradiol modulates GH secretion and suppresses IGF-1 production. These hormonal dynamics fosterf a balance essential for normal pubertal progression and contributes to the transient nature of pubertal gynecomastia [41]. Other laboratory analyses might be required according to clinical suspicion (Table 2).

Remarks

When laboratory assessment is needed, it should follow a structured approach. Morning testosterone measurement is recommended, alongside SHBG and albumin to calculate free and bioavailable testosterone. Measurement of estradiol may be considered in selected clinical scenarios suggestive of estrogen excess or hormone-secreting conditions. However, its clinical interpretation is limited by the lack of validated thresholds and by methodological issues related to commonly used assays, favoring more reliable techniques such as LC/MS. Further hormonal investigations should include LH, prolactin, as well as tumor markers (hCG and α-fetoprotein) when testicular malignancy is suspected. In selected cases, additional tests may be warranted based on clinical suspicion, including TSH, IGF-1, renal and liver function along with infectious disease serologies (HIV, HCV, HBV), adrenal precursors such as 17-hydroxyprogesterone and androstenedione, especially when androgen excess or adrenal enzyme defects are suspected.

Imaging and core needle biopsy

Recommendations

R1 *We recommend breast imaging to assess gynecomastia when physical examination is equivocal or suspicious for breast cancer (1 ØØØØ).*

R2 *We suggest ultrasound as the initial imaging study of male breast, especially in men younger than age 35, and eventually in men younger than age 45 (2 ØØØO).*

R3 *We suggest using ultrasound beside physical examination and gynecomastia-related symptoms and duration assessment to better plan medical therapy and monitor its efficacy over time (2 ØØOO).*

R4 *We recommend mammography if physical examination is strongly suspicious and/or ultrasound doubtful for breast cancer, prior to core needle biopsy (1 ØØØØ).*

R5 *We recommend core needle biopsy when physical examination and mammography outcomes are strongly suspicious for malignancy, and ultrasound can assist in lesion characterization and guide core needle biopsy (1 ØØØØ).*

R6 *We recommend clinical and ultrasound evaluation of the testes to exclude a palpable or non-palpable testicular tumor when gynecomastia is confirmed (1 ØØØO).*

Evidence

The most recent "American College of Radiology (ACR) Appropriateness Criteria for the evaluation of the symptomatic male breast" [128] report that: (i) in men with clinical findings consistent with gynecomastia or pseudogynecomastia, no imaging is routinely recommended; (ii) if an indeterminate breast mass is identified, the initial recommended imaging study is ultrasound (US) in men younger than age 25, and mammography or digital breast tomosynthesis in men aged 25 and older; (iii) if physical examination is suspicious for a male breast cancer, breast imaging is recommended prior to core needle biopsy, mammography is recommended as the initial imaging modality regardless of age, and ultrasound can assist in lesion characterization and guide core needle biopsy.

So far, it has been reported that most men with gynecomastia and related symptoms can be diagnosed by physical examination without imaging [30, 67, 74]. Physical examination represents the cornerstone of the diagnostic evaluation of male breast enlargement. In most patients, careful clinical assessment allows the clinician to distinguish gynecomastia from pseudogynecomastia and to identify features suggestive of malignancy. In particular, physical examination shows high sensitivity and negative predictive value for excluding breast cancer when typical benign features are present. Gynecomastia is the most common cause of a palpable mass, breast enlargement, or pain [128–131] and is bilateral in approximately half of patients [128]. Clinically, it often presents as a soft, rubbery, or firm mobile mass under the nipple [6, 129]. It has been suggested to quantitatively diagnose it by physical examination as a subareolar breast tissue ≥ 2 cm in transversal diameter [3, 6].

The most common differential diagnosis of gynecomastia at physical examination is pseudogynecomastia, relatively frequent in overweight and obese men and difficult to distinguish from true gynecomastia [4, 132]. Hence, when physical examination is equivocal in distinguishing the two conditions, ultrasound is suggested.

On the other hand, the most important life-threatening differential diagnosis of gynecomastia is breast cancer., which predominantly affects older men [131]. It is usually unilateral and typically presents with a painless, hard mass, which may be subareolar or, unlike gynecomastia, eccentric to the nipple [128, 131]. With breast cancer, there may be secondary signs of malignancy, such as nipple or skin retraction, nipple discharge, or axillary lymphadenopathy [128, 131, 133]. Breast cancers in men often present at a later age (105) and a more advanced stage than in women, with up to 47% of men having axillary nodal involvement at the time of diagnosis [128, 133]. In addition, nipple discharge is suspicious for breast cancer in men, with two studies showing carcinoma in 23% to 57% of men presenting with this symptom [134, 135]. Conversely, only 6% of male breast cancers occur in men <45 years of age and $<1\%$ in men <35 years of age [136].

It has been reported that breast physical examination in men lacks specificity in the detection of malignancy [137]. One study on 628 male patients reported a positive predictive value (PPV) for cancer detection of 19.2% [129]. Other studies reported a PPV of 8%–55% [137, 138]. Therefore, physical examination should be considered the first diagnostic step, and imaging should be reserved for cases with equivocal findings or features suspicious for malignancy [137].

However, only a few studies determined and compared the diagnostic performance of physical examination, US and mammography in evaluating the male breast and differentiating gynecomastia from cancer. In particular, one study [129] found that the diagnostic performance of physical examination was lower than that of US and mammography ($p<0.05$ for specificity). In addition, US was the most specific (95.3%) and mammography the most sensitive (94.7%) for detection of malignancy ($p>0.05$). US and mammography, with a negative predictive value (NPV) close to 100%, make it possible to avoid many unnecessary surgical procedures in men [129]. Hence, when a breast mass is detected at physical examination, imaging is very useful to increase the diagnostic accuracy and for differential diagnosis.

For men with a physical examination strongly suspicious for malignancy, mammography is recommended as the best imaging tool because it has high sensitivity, specificity, and negative predictive value (NPV) for breast cancer diagnosis [128, 130, 131]. If mammography is indeterminate or suspicious, US can assist in lesion characterization and guide biopsy [128].

Although some Authors [129] suggest using US as the initial imaging modality in the "young" male < 25 years old according to ACR [128] or < 35 years old according to Giordano et al. [136]) with an "indeterminate" physical examination, since he is unlikely to have breast cancer, mammography shows a higher accuracy for breast cancer diagnosis, and should be performed before any biopsy [128]. Hence, while US should represent the initial imaging modality in "young" men to assess gynecomastia when physical examination is equivocal, when physical examination is strongly suspicious for malignancy mammography represents the imaging modality of choice prior to core needle biopsy at any age.

Remarks

The ACR recommendations [128] are mainly focused on ruling out breast cancer diagnosis than assessing gynecomastia. However, gynecomastia has a significant higher prevalence than breast cancer [136] and deserves specific recommendations on its assessment.

The most common differential diagnosis of gynecomastia is pseudogynecomastia, while the most relevant for general health is male breast cancer [132]. While pseudogynecomastia is relatively frequent and benign, malignancy is very rare but life-threatening. In particular, male breast cancer is virtually absent below the age of 35 [136]. Its prevalence is 5.5% in men aged 35–44 years, increasing especially in men older than 45 years old [136], with a median age at diagnosis of 63 years [131].

To provide differential diagnosis, US and mammography have been previously considered. US is a simple, rapid and harmless diagnostic tool, not using radiations as mammography, and, among imaging techniques, is the least expensive [139]. In addition, an US console is often available to the clinicians (including endocrinologists and andrologists) in outpatient clinics, making its use simple during a medical visit and easier than to resort to other imaging techniques in charge of radiologists.

According to the aforementioned statements, if an indeterminate breast mass is identified at physical examination, the initial suggested imaging study should be US, especially in men younger than age 35 (and eventually in men younger than age 45) instead of mammography, that could be associated to US when the latter is doubtful.

Special attention should be given both at physical examination and imaging to white and, secondly, black men, at higher risk of breast cancer than other subjects [136, 140]. In addition, patients with Klinefelter Syndrome (KS) deserve high attention for male breast cancer risk [141, 142]. A meta-analysis of case-control studies reported a prevalence of breast cancer in KS of about 3% [143], while its prevalence is rare in non-KS men (0.6% of all breast carcinomas and < 1% of all malignancies in men) [142]. KS subjects showed a 30- to 50-times higher risk than the general male population [141, 144]. A recent meta-analysis [145] confirmed KS as significantly associated with breast cancer (OR = 24.7; 95% CI = 8.94 to 68.4). Hence, annual breast clinical examination, and imaging when physical examination is equivocal, is recommended in KS men.

The US diagnosis of gynecomastia describes three main patterns (with definitions derivable from mammography), including "nodular", "dendritic" and "diffuse", and US allows differential diagnosis especially with pseudogynecomastia [132, 137, 146] (Fig. 2). Nodular gynecomastia occurs in the early (florid) phase of gynecomastia and appears at US as a subareolar fan- or disk-shaped area of hypoechoic tissue. It typically correlates with symptomatic duration of < 1 year [137]. Dendritic gynecomastia occurs with long-standing gynecomastia (quiescent phase) that has been present for 1 year or longer. It typically presents as a serpiginous hypoechoic area with finger-like projections in the subareolar region [137]. Diffuse gynecomastia is usually seen in the setting of high-dose estrogen therapy or exogenous hormone use. On US, there is increased volume and echogenicity of breast tissue, identical to female breasts [137]. Finally, pseudogynecomastia is characterized by increased subareolar fat without enlargement of the breast glandular component [137].

In order to guide the physician for wait and see, medical or surgical treatment, US can be useful to indicate the "pattern" of gynecomastia, especially when symptomatic duration of gynecomastia is not clear. In fact, the nodular pattern, occurring in the florid phase of gynecomastia, can show spontaneous regression in adolescents and/or is more sensitive to medical therapy, while the dendritic pattern, related to the quiescent phase, is less responsive [6, 137]. In addition, US is more accurate than physical examination to evaluate changes of breast tissue overtime or under medical treatment and could be considered along with physical and symptoms changes to guide the duration of the wait and see phase or of the medical treatment. Furthermore, US can be useful to differentiate true gynecomastia and pseudogynecomastia when physical examination is doubtful, especially in overweight and obese men [132, 146].

However, so far, the US diagnosis of gynecomastia is mainly qualitative, and only one study [147] reported a

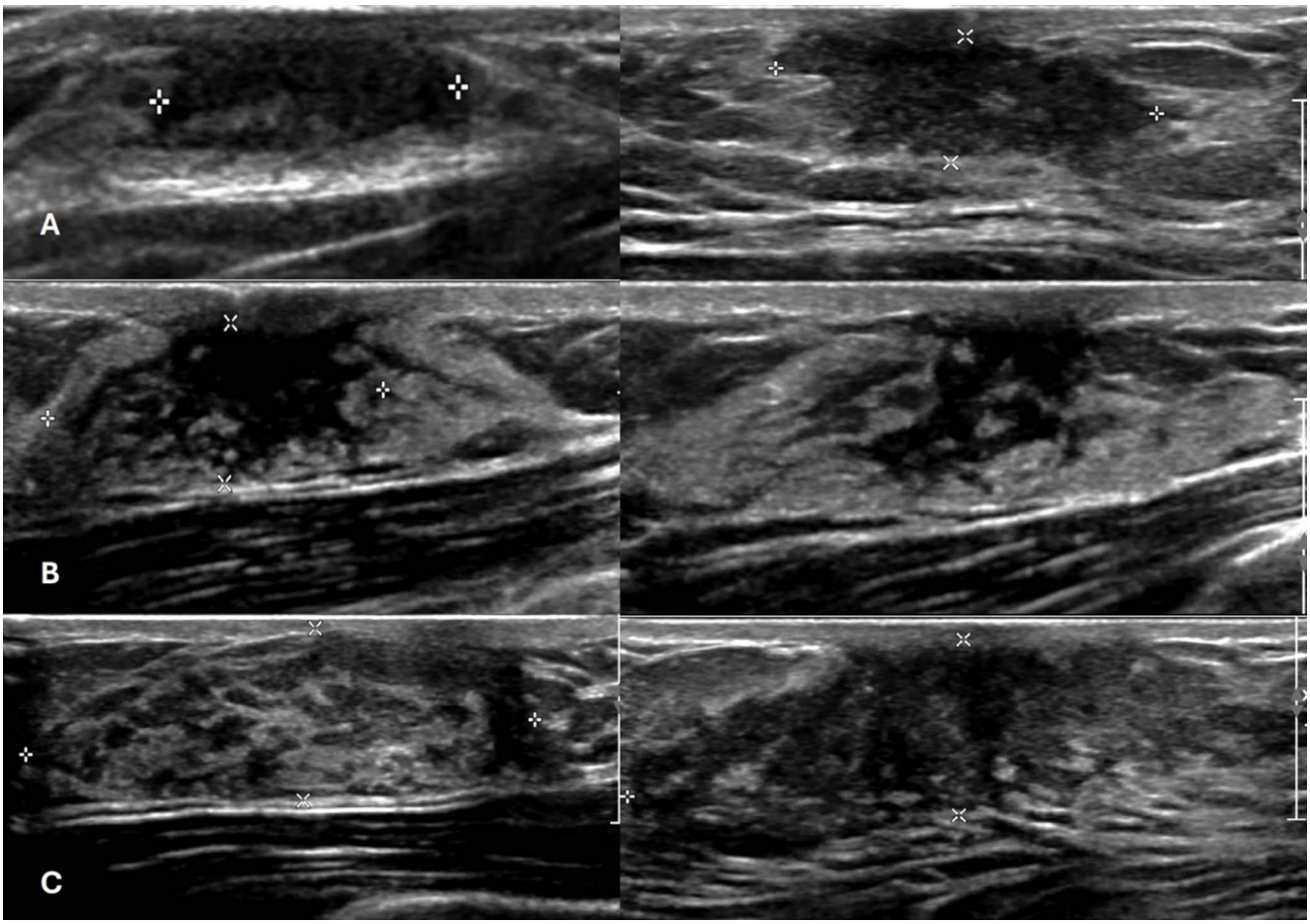


Fig. 2 Ultrasound patterns of gynecomastia **Panel A**: Ultrasound scan showing grade I (nodular pattern) gynecomastia, characterized by a hypoechoic, well-defined retroareolar mass. This pattern typically corresponds to the early/florid phase of gynecomastia, is often tender and is associated with recent onset (less than 6 months. **Panel B**: Grade II (dendritic pattern) gynecomastia, presenting as a hypoechoic area with finger-like projections radiating into the surrounding tissue, resembling a dendritic tree. This pattern corresponds to the intermediate/fibroglandular phase, with partial proliferation of fibrous tissue. It is usually less tender, indicating subacute progression. **Panel C**: displays a grade III gynecomastia (diffuse pattern), characterized by heterogeneous, diffuse increase in echogenicity, without clear margins. It reflects the chronic (fibrotic) phase of gynecomastia, and it is typically non-tender and often associated with long-standing cases

quantitative, not evidence-based, definition, suggested as increased breast tissue defined as "anteroposterior depth > 1 cm from the skin surface under the nipple to the anterior surface of the pectoralis muscle". In addition, no threshold for a diagnostic transversal diameter at US is available, while a threshold of this diameter (≥2 cm) is used in clinical practice for a physical examination-based diagnosis [3]. Finally, the definition of "normal" breast tissue is only suggested, but not evidence-based [132, 146]. Hence, a quantitative standardization of gynecomastia at US is advocated. Finally, when gynecomastia is confirmed, several evidence [6, 62, 146, 148] and available guidelines [4] indicate to perform clinical and US evaluation of the testes to exclude a palpable or non-palpable testicular tumor. Testicular US is advocated as the detection of a testicular tumor by palpation has low sensitivity [4]. On the other hand, when physical examination is strongly suspicious for a male breast cancer, breast imaging and core needle biopsy are recommended (see Recommendations). The importance of preoperative histological diagnosis in the assessment of breast lesions in women is widely established, but in men with breast lesions histological diagnosis is obtained in a limited number of cases [149]. The main reason is probably related to the low incidence of breast cancer in men: male breast cancer accounts for only 1% of breast cancer diagnoses in the USA and less than 0.1% of cancer-related deaths in men [150]. Despite its rarity, incidence of male breast cancer has increased over the past three decades, and for this reason it is increasingly important to achieve a preoperative pathological diagnosis using core needle biopsy or fine-needle aspiration cytology [151]. While fine-needle aspiration yields quite a high rate (13–15%) of inadequate specimens [152, 153], core needle biopsy allows sufficient tissue for diagnosis and represents an effective method in

distinguishing benign and neoplastic lesions in the male breast [149, 151, 152]. In fact, core needle biopsy allows histological examination, which is mandatory if malignancy is suspected [3, 149, 151, 152].

Clinical management

Watchful waiting

Recommendations

R1 *We recommend watchful waiting for at least 6 months after resolution of the underlying secondary causes of gynecomastia prior to considering any medical or surgical treatment (1 ØØOO).*

R2 *We recommend watchful waiting for new-onset pubertal gynecomastia with duration of follow-up not exceeding 2 years and still to be determined on a case-by-case basis depending on psychological burden and gynecomastia severity (1 ØØØO).*

Evidence

The culprit medications should be discontinued, when possible, based on careful evaluation of cost-benefit ratio. If gynecomastia is suspected to be caused by abuse of exogenous substances, then withdrawal of the inciting agent(s) should be encouraged. Improvement should be evident within one month after discontinuation [6]. If gynecomastia secondary to comorbidities, medical therapies, and use/abuse of exogenous agents has lasted for more than 6 months, regression is unlikely due to the presence of less reversible fibrotic tissue [7]. In cases of pubertal gynecomastia, as well as newly onset adulthood idiopathic gynecomastia, a wait-and-see approach may be recommended because most cases may resolve spontaneously [154]. However, there remains uncertainty about the duration of the wait-and-see attitude. In the few available longitudinal studies, physiological pubertal gynecomastia exhibited a duration of 1 to 2 years [42, 155, 156], while one study reported that in 60% of boys, gynecomastia lasted less than 6 months [157]. Approximately only 20% of boys persist with residual breast enlargement at the age of 20 years [7].

Remarks

In physiologic gynecomastia, follow-up should include clinical assessments every 3–6 months [154], setting decision-making strategies on whether and when to intervene on an individualized basis, taking into account the psychological burden and clinical severity of gynecomastia [158]. In severe and/or long-lasting forms with no tendency for remission within 2 years, the increase in stromal hyalinization and inactive fibrotic tissue [159] makes the efficacy of any medical therapy unrealistic, placing an indication for surgical treatment [154].

Medical treatment

Recommendations

R1 *We recommend prescribing testosterone therapy in men with gynecomastia only in the presence of proven androgen deficiency (1 ØØØØ).*

R2 *We suggest a short course (3–6 months) of treatment with Tamoxifen (20 mg/day) in selected cases of idiopathic gynecomastia of recent onset (< 6 months) before resorting to the surgical option in case of failure (Expert Opinion).*

R3 *We suggest a short course (1–3 months) of transdermal dihydrotestosterone (DHT) 2.5% in selected cases of idiopathic gynecomastia of recent onset (< 6 months) before resorting to the surgical option in case of failure (Expert Opinion).*

R4 *We do not recommend prescribing aromatase inhibitors (AIs), danazol or nonaromatizable androgens in the treatment of gynecomastia (1 ØØOO).*

R5 *We suggest the use of tamoxifen (10–20 mg daily) to prevent bicalutamide-induced gynecomastia and/or breast pain in patients with prostate cancer (2 ØØOO).*

R6 *We suggest the use of radiotherapy (10 to 15 Gy) to prevent bicalutamide-induced gynecomastia but not mastodynia in patients with prostate cancer (2 ØOOO).*

R7 *We recommend not prescribing AIs for preventing bicalutamide-induced breast events in patients with prostate cancer (1 ØØOO).*

Evidence

In men with proven androgen deficiency, testosterone replacement therapy can improve gynecomastia as well as the other clinical features of hypogonadism [160]. On the contrary, in eugonadal men, aromatization of excess exogenous testosterone to estradiol may exacerbate or even induce breast enlargement [20]. No RCTs are available on the effect of nonaromatizable androgens, although percutaneous treatment with dihydrotestosterone has shown some efficacy in small series of patients [87, 161, 162].

Many other drugs have been tested as possible medical treatments for gynecomastia in uncontrolled trials or series of cases. These included selective estrogen receptor modulators (SERMs) [163–169], antiestrogens with weak androgenic activities, such as danazol [163, 170, 171] and AIs such as testolactone [172] or anastrozole [169, 173, 174].

Table 3 Main characteristics of available RCTs on nonsurgical treatments in preventing breast events in patients with prostate cancer undergoing androgen ablation therapy with bicalutamide (150 mg daily)

RCT	Arms	Gynecomastia assessment	Breast pain assessment	Follow-up (months)
Widmark et al. [160]	Bica alone ($n=79$) or with RT 12 to 15 Gy in a single fraction or 15 Gy in 3 fractions ($n=174$)	Physical examination	Physical examination, self-reported, questionnaire	12
Tyrrell et al. [161]	Bica with sham ($n=54$) or with a single 10 Gy RT dose ($n=52$)	Callipers	Self-reported	12
Boccardo et al. [154]	Bica with Placebo ($n=40$) or Tam 20 mg daily ($n=37$) or Anas 1 mg daily ($n=36$)	Callipers And ultrasound	Self-reported	Median: 12 (1 to 25)
Di Lorenzo et al. [155]	Bica alone ($n=33$) or with Tam 10 mg daily ($n=34$) or a single 12 Gy RT dose ($n=35$)	Callipers	Self-reported	Median: 26 (13 to 35)
Perdonà et al. [157]	Bica alone ($n=51$) or with Tam 10 mg daily ($n=50$) or a single 12 Gy RT dose ($n=50$)	Callipers	Self-reported	12
Saltzstein et al. [158]	Bica with Placebo ($n=36$) or Tam 20 mg daily ($n=34$) or Anas 1 mg daily ($n=36$)	Physical examination	Questionnaire	9
Fradet et al. [156]	Bica with Placebo ($n=60$) or Tam 1 ($n=58$), 2.5 ($n=45$), 5 ($n=47$), 10 ($n=34$) or 20 mg ($n=34$)	Callipers	Self-reported	12
Ozen et al. [162]	Bica alone ($n=61$) or with RT 12 Gy dose in 2 fractions of 6 Gy each on consecutive days ($n=44$)	Callipers	Self-reported	12
Serretta et al. [159]	Bica alone ($n=83$) or with Tam 10 mg daily ($n=80$)	Self-reported (VAS)	Self-reported (VAS)	Median: 15 (12 to 36)

Anas, anastrozole; Bica, bicalutamide; RCT, randomized, controlled trial; RT, radiotherapy; Tam, tamoxifen; VAS, visual analogue scale

Despite often encouraging results, unfortunately, the uncontrolled design makes it impossible to draw firm conclusions, as gynecomastia can also resolve spontaneously. Randomized, placebo-controlled, double-blind trials that have evaluated the effects of SERMs, namely tamoxifen (10 mg twice daily), in patients with idiopathic gynecomastia are limited to two older, small crossover studies [175, 176].

In the study by Parker et al. [175], 7 out of 10 patients had a reduction in gynecomastia size with tamoxifen ($p<0.005$), and all 4 with pain reported relief. McDermott et al. [176] found that tamoxifen significantly reduced pain in 5 out of 6 patients, while no improvements were seen in the placebo group ($p=0.04$). Breast size reduction was observed in 3 tamoxifen-treated patients, but the difference was not statistically significant ($p=0.09$).

The effect of other medical therapies in idiopathic gynecomastia has been evaluated in scanty RCTs. In a randomized double-blind study of 52 patients with idiopathic gynecomastia [177], treatment for 3 months with danazol (200 mg twice daily) significantly improved breast tenderness compared with placebo ($P=0.022$) and was associated with significant reduction in the degree of gynecomastia and its measured size ($P<0.05$). In the same study, danazol also reduced the likelihood of surgical treatment but significantly increased body weight.

A more recent randomized, double-blind, placebo-controlled trial assessed the possible utility of anastrozole for the treatment of pubertal gynecomastia [169]. Eighty boys aged 11–18 years with pubertal gynecomastia received anastrozole (1 mg) or placebo once daily for 6 months. The percentage of patients with a response (at least 50% reduction in breast ultrasound volume) was 38.5% for the anastrozole arm and 31.4% for the placebo arm, a statistically nonsignificant difference (OR: 1.51; 95%CI: 0.49 to 4.84). At present the use of AIs is indicated only for aromatase excess syndrome, a genetic cause of gynecomastia (see above the paragraph on genetic causes of gynecomastia).

More evidence is available on the role of nonsurgical treatments in preventing gynecomastia and/or breast pain in patients with prostate cancer undergoing androgen ablation therapy (AAT) with bicalutamide. As shown in Table 3, to date, the efficacy of prophylactic treatment with tamoxifen for this indication, albeit not approved by the Food and Drug Administration, has been evaluated in six randomized trials [178–183], including three double-blind placebo-controlled trials [178, 180, 182]. In some of these studies, the prophylactic efficacy of anastrozole [178, 182] and radiotherapy [179, 181] was also evaluated. Radiotherapy was also used in additional 3 RCTs [184–186]. In the study by Boccardo et al. [178], patients with prostate cancer on bicalutamide were randomized to receive placebo, tamoxifen, or anastrozole. Gynecomastia occurred in 33% of the placebo group, 17% in the anastrozole group, and none in the tamoxifen group. Breast pain was also more frequent in the placebo group (39%). Similarly, Di Lorenzo et al. found that tamoxifen significantly reduced gynecomastia and breast pain

compared to bicalutamide alone [179]. In a subsequent RCT [181], bicalutamide alone caused gynecomastia in 35 of 51 patients, while tamoxifen reduced this to 4 of 50. Fradet et al.'s trial [180] showed a dose-dependent effect of tamoxifen, with 81.7% of placebo patients developing gynecomastia compared to 14.7% in the 20 mg tamoxifen group. Saltzstein et al. [182] found that tamoxifen, but not anastrozole, reduced gynecomastia and pain. Serretta et al. [183] observed a significant reduction in gynecomastia and pain with tamoxifen. Additionally, radiotherapy has been shown to help prevent gynecomastia [184], though it was ineffective in preventing breast pain in some studies [185, 186].

Remarks

The available evidence on the efficacy of medical therapies in idiopathic gynecomastia and associated chest pain is insufficient to draw any firm conclusion. Although not approved for this indication, of some usefulness may be tamoxifen at a dose of 20 mg daily [187], or DHT 2.5% daily application [3, 87, 161, 188, 189] in cases of painful gynecomastia of recent onset to offer pain relief and, occasionally, partial regression of the breast enlargement. For these pharmacological treatments an informed consent is imperative as they are off label. The grading of the evidence is possible for nonsurgical therapies, namely tamoxifen, anastrozole, and radiotherapy, when used as prophylaxis of breast events in men with prostate cancer undergoing AAT with bicalutamide [190, 191].

Although all RCTs on tamoxifen have produced results in the same direction indicating its efficacy in preventing both AAT-induced gynecomastia and breast pain, a number of limitations reduce the quality of the evidence supporting the recommendation. First, the evidence is downgraded by the low number of RCTs, involving few patients and documenting few outcomes with quite wide confidence intervals. The low precision prevents the achievement of adequate statistical power of the overall effect estimates. Second, a methodological limitation arises from a possible attrition bias because not in all available RCTs the dropout rate was appropriately reported; however, when specified, it was below 20% [180, 182, 183]. Third, an obvious heterogeneity between the studies reflected differences in tamoxifen doses (10 mg or 20 mg per day) and duration of treatment (varying from 3 to 12 months). Finally, it is difficult to evaluate the efficacy of a drug since gynecomastia may resolve spontaneously. Treatment regimens remain largely empirical, and in the absence of comparative studies, no recommendation can be made for one dosage over another. In an open multicenter randomized phase 3 trial [192], daily treatment with tamoxifen 20 mg was superior to the scheme with tamoxifen 20 mg weekly (after 8 weeks of daily therapy) in preventing bicalutamide-induced gynecomastia and breast pain. As for anastrozole, the 2 available RCTs [178, 182] agreed in recognizing its ineffectiveness in preventing bicalutamide-induced breast events in patients with prostate cancer. On the contrary, in these patients, some prophylactic efficacy on the occurrence of gynecomastia, but not mastodynia, seems attributable to radiotherapy [179, 181, 184–186]. Nevertheless, the availability of only one sham-controlled RCT [185], along with differences in doses (10 to 15 Gy) and treatment modalities, downgraded the overall quality of the evidence.

Medical treatment of genetic and congenital causes of gynecomastia

R8 *We suggest treating children with documented aromatase excess syndrome with aromatase inhibitors and those with congenital adrenal hyperplasia with hydrocortisone, in order to correct the underlying endocrine disorder and improve gynecomastia (2 ØØØØ).*

R9 *We suggest treating the underlying clinical condition in case of congenital hypogonadotropic hypogonadism and of defects of steroid biosynthesis which may contribute to the improvement of gynecomastia (2 ØØØO).*

Evidence

The aromatase inhibitor anastrozole at the dose of 1.0 mg daily is effective in normalizing serum estrogens [21], promoting growth in order to reach a final height close the genetic target and gynecomastia disappearance [96, 108].

Treatment with hydrocortisone substitution at the dose of 12.5 mg/m2/day in boys with non-classical 21-hydroxylase deficiency or 11β-Hydroxylase may completely regress gynecomastia in 5–8 months after the start of therapy [103–105].

Treatment of gynecomastia in patients with ovotestis depends on multidisciplinary consensus about the final goal concerning phenotypic sex. Thus, mammary tissue should be surgically removed in case of development towards an adult male phenotypic aspect [109].

Remarks

The treatment of gynecomastia in the context of rare genetic or congenital diseases is complex and should be based on the best practice approach available for the disease, considering also the main objectives of the therapy beyond gynecomastia.

Surgical treatment

Recommendations

R1 *We recommend surgical treatment for patients with long-lasting fibrotic gynecomastia with no tendency to spontaneous regression and no response to appropriate medical therapy, especially in the presence of psychological distress (1 ØØOO).*

R2 *We recommend tailoring the surgical technique on a case-by-case basis, according to the severity degree, the amount of fatty tissue and the surgeon's experience (1 ØØØO).*

Evidence

Although most patients with gynecomastia will experience its spontaneous resolution after medical treatment or following elimination of the underlying cause, a small proportion of cases with persistent or refractory gynecomastia will require surgery. Need, time and type of surgery should be defined based on the severity of breast enlargement and psychological implications.

Surgery should be performed by an experienced surgeon because there is a risk of cosmetic complications due to residual scarring and asymmetry. Different techniques have been proposed with an individualized approach [193], including semicircular, inframammary, intra-areolar, or axillary incision [194, 195], glandular and adipose tissue excision combined with liposuction [154, 196, 197]. It is critical to retain some subareolar tissue and subcutaneous vascular plexus to ensure sufficient blood supply, avoiding nipple necrosis and retraction [194, 198]. Depending on the size of the gynecomastia, reduction surgery may be indicated [197].

Remarks

Although a reasonable observation period is always necessary before surgical treatment is offered, if gynecomastia has persisted for more than 6–12 months, it is unlikely to regress due to the presence of fibrosis. Nevertheless, in the case of pubertal gynecomastia, regression can occur up to 2 years [42, 155, 156]. Surgical treatment for pubertal gynecomastia should be postponed after the end of puberty to minimize the risk of recurrence after surgery [199] apart from cases characterized by severe psychological distress.

Psychological/cosmetic treatment

Recommendations

R1 *We suggest screening for psychological distress in men with gynecomastia, especially adolescents and young adults (2 ØØOO).*

R2 *We suggest proposing psychological counseling in men with gynecomastia and provide psychological support in selected cases before and after eventual surgical or cosmetic treatments (2 ØOOO).*

R3 *We suggest aesthetic or reconstructive surgical treatments in men with gynecomastia-related severe psychological distress, especially adolescents and young adults (2 ØØOO).*

Evidence

Gynecomastia may have relevant psychological and psychosocial consequences. A systematic review on psychosocial aspects of gynecomastia in adolescents and young men [113] identified a variety of psychosocial correlates of gynecomastia. These included several anecdotal negative "opinions" of varying severity, going from feeling embarrassed to suicidal despair [113]. Psychosocial correlates that were measured using psychometrically sound instruments included anxiety, depression, and health-related quality of life [113]. Another review [200] confirmed the association of gynecomastia with depression, anxiety, low self-esteem and body image concerns, issues that may lead patients to maladaptive coping mechanisms.

A few studies with low quality and strength of evidence [113], suggest routine screening for psychological distress [201] as well as psychotherapy [202]/mental health treatment [203] in the management of adolescents with gynecomastia. A few studies reported that when gynecomastia causes considerable cosmetic and psychological distress, surgical treatment is justified [113, 196, 204]. A recent systematic review [205] reported that for many patients the psychological impact of gynecomastia is substantial, and supported improvement in quality of life and several psychological domains after surgical treatment of gynecomastia.

Besides surgical treatment, cosmetic treatment of gynecomastia can be considered. So far, minimally invasive procedures to correct aesthetic problems of male breast are available. The major indications are gynecomastia, breast asymmetry, and body sculpturing [206]. Minor surgery, including current treatments combining subcutaneous fat and breast tissue excision, laser lipolysis, dermal filler and cell-assisted lipotransfer are among the most promising techniques available [206, 207].

Remarks

Most of the available literature on the topic refers to adolescents or young men, while other populations, including older men or iatrogenic gynecomastia are less represented [4, 203].

The evidence regarding the psychological and psychosocial consequences of gynecomastia is poor. Considering one aforementioned systematic review [113], overall, the articles reviewed included small samples. All studies were limited to single sites. Several studies included no or limited statistical analyses of the data. The population estimates for gynecomastia and its correlates varied widely within the reports.

Regarding psychosocial interventions, they included vague terms such as psychotherapy, mental health treatment, and early intervention to improve both physical and emotional symptoms [113]. In addition, no study reported the development or testing of psychosocial interventions specifically designed for young males with gynecomastia [113, 208]. Finally, although improvement in quality of life and several psychological domains after surgical treatment for gynecomastia has been reported by a systematic review, the level of evidence on this topic is very low.

Regarding cosmetic treatments (as well as surgery), the male breast is of increasing interest in esthetic surgery in general and for minimally invasive techniques in particular [207]. Gynecomastia is perceived by men as a stigmatizing disease [207]. Cosmetic treatments should be considered especially in adolescents and young adults with severe psychological distress. Adolescence is a very critical period where self-esteem is formed and where it is easier to be teased by peers, and physicians should consider surgical or cosmetic therapeutic options, eventually assisted by psychological counseling.

Conclusions and future directions

Gynecomastia represents a complex clinical condition arising from diverse etiologic pathways, ranging from physiological hormonal shifts to pathological endocrine imbalances and iatrogenic causes. It often resolves spontaneously in physiological cases but may require further investigation and management in pathological or drug-induced cases. Effective diagnosis and treatment involve understanding the underlying causes, considering patient age, possible psychological and physical burden on patients and evaluating risk factors. Our aim was to address this gap by proposing a standardized diagnostic and therapeutic approach grounded in current evidence and expert consensus. However, several unmet needs persist. First, high-quality prospective studies are still lacking in many areas, including the natural history of persistent pubertal gynecomastia, the comparative effectiveness of medical therapies, and long-term outcomes of surgical intervention. Furthermore, the psychosocial impact of gynecomastia, frequently underestimated, deserves more structured assessment tools and integrated care pathways involving psychological support when appropriate. In future research, the role of novel imaging techniques and minimally invasive diagnostic strategies should be further explored. Given the increasing exposure of the general population to endocrine-disrupting chemicals and off-label use of anabolic agents, epidemiological surveillance and public health initiatives will be crucial to mitigate emerging risks. Finally, patient-centered care should remain the guiding principle: clinical decisions should not only be evidence-based, but also tailored to the individual's age, comorbidities, expectations, and quality of life concerns. The development of multidisciplinary networks, combining endocrinologists, andrologists, pediatricians, surgeons, and mental health professionals, will be essential to ensure comprehensive and compassionate care for patients with gynecomastia.

Author contributions Conceptualization and supervision: CP, VR, RS. Methodology and coordination of the guideline development: CP, VR, RS. Literature review: All authors. Drafting of manuscript sections: Introduction: DP; Methods: CP, VR, RS; Pathophysiology: AS; Causes of gynecomastia: CP, VH, DM, VR; Clinical evaluation: DM; Laboratory assessment: AS; Imaging and core needle biopsy: FL; Clinical and surgical management: AB; Psychological aspects: FL. Critical revision of the manuscript for important intellectual content: All authors. All authors participated in the development of the recommendations and approved the final version of the manuscript.

Funding No specific funding was used in relation to this manuscript.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable to this kind of paper.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory

regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Swiglo BA, Murad MH, Schunemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM (2008) A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. J Clin Endocrinol Metab 93(3):666–673. https://doi.org/10.1210/jc.2007-1907
2. De Sanctis V, Soliman AT, Tzoulis P, Daar S, Di Maio S, Kattamis C (2023) Unilateral breast enlargement in males during adolescence (10–19 years): Review of current literature and personal experience. Acta Biomed 94(2):e2023004. https://doi.org/10.23750/abm.v94i2.14324
3. Swerdloff RS, Ng JCM (2000) Gynecomastia: Etiology, Diagnosis, and Treatment. In: *Endotext.* edn. Edited by Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J South Dartmouth (MA)
4. Kanakis GA, Nordkap L, Bang AK, Calogero AE, Bartfai G, Corona G, Forti G, Toppari J, Goulis DG, Jorgensen N (2019) EAA clinical practice guidelines-gynecomastia evaluation and management. Andrology 7(6):778–793. https://doi.org/10.1111/andr.12636
5. Mieritz MG, Christiansen P, Jensen MB, Joensen UN, Nordkap L, Olesen IA, Bang AK, Juul A, Jorgensen N (2017) Gynaecomastia in 786 adult men: clinical and biochemical findings. Eur J Endocrinol 176(5):555–566. https://doi.org/10.1530/EJE-16-0643
6. Braunstein GD (2007) Clinical practice. Gynecomastia. N Engl J Med 357(12):1229–1237. https://doi.org/10.1056/NEJMcp070677
7. Narula HS, Carlson HE (2014) Gynaecomastia–pathophysiology, diagnosis and treatment. Nat Rev Endocrinol 10(11):684–698. https://doi.org/10.1038/nrendo.2014.139
8. Nuttall FQ (2010) Gynecomastia. Mayo Clin Proc 85(10):961–962. https://doi.org/10.4065/mcp.2010.0093
9. Berger O, Hornik-Lurie T, Talisman R (2024) Pubertal gynecomastia incidence among 530,000 boys: a cross sectional population based study. Front Pediatr 121367550. https://doi.org/10.3389/fped.2024.1367550
10. Guss CE, Divasta AD (2017) Adolescent Gynecomastia. Pediatr Endocrinol Rev 14(4):371–377. https://doi.org/10.17458/per.vol14.2017.GD.Gynecomastia
11. Costanzo PR, Pacenza NA, Aszpis SM, Suarez SM, Pragier UM, Usher JGS, Vasquez Cayoja M, Iturrieta S, Gottlieb SE, Rey RA, Knoblovits P (2018) Clinical and Etiological Aspects of Gynecomastia in Adult Males: A Multicenter Study. Biomed Res Int 20188364824. https://doi.org/10.1155/2018/8364824
12. Iuanow E, Kettler M, Slanetz PJ (2011) Spectrum of disease in the male breast. AJR Am J Roentgenol 196(3):W247–259. https://doi.org/10.2214/AJR.09.3994
13. Safak KY (2015) Mammography Findings of Male Breast Diseases. J Breast Health 11(3):106–110. https://doi.org/10.5152/tjbh.2015.2565
14. Ladizinski B, Lee KC, Nutan FN, Higgins HW 2nd, Federman DG (2014) Gynecomastia: etiologies, clinical presentations, diagnosis, and management. South Med J 107(1):44–49. https://doi.org/10.1097/SMJ.0000000000000033
15. Nuttall FQ, Warrier RS, Gannon MC (2015) Gynecomastia and drugs: a critical evaluation of the literature. Eur J Clin Pharmacol 71(5):569–578. https://doi.org/10.1007/s00228-015-1835-x
16. Rohayem J, Alexander EC, Heger S, Nordenstrom A, Howard SR (2024) Mini-Puberty, Physiological and Disordered: Consequences, and Potential for Therapeutic Replacement. Endocr Rev 45(4):460–492. https://doi.org/10.1210/endrev/bnae003
17. Jayasinghe Y, Cha R, Horn-Ommen J, O'Brien P, Simmons PS (2010) Establishment of normative data for the amount of breast tissue present in healthy children up to two years of age. J Pediatr Adolesc Gynecol 23(5):305–311. https://doi.org/10.1016/j.jpag.2010.03.002
18. Bowman JD, Kim H, Bustamante JJ (2012) Drug-induced gynecomastia. Pharmacotherapy 32(12):1123–1140. https://doi.org/10.1002/phar.1138
19. Ikard RW, Vavra D, Forbes RC, Richman JC, Roumie CL (2011) Management of senescent gynecomastia in the Veterans Health Administration. Breast J 17(2):160–166. https://doi.org/10.1111/j.1524-4741.2010.01050.x
20. Johnson RE, Murad MH (2009) Gynecomastia: pathophysiology, evaluation, and management. Mayo Clin Proc. 84(11):1010–1015. https://doi.org/10.1016/S0025-6196(11)60671-X
21. Shozu M, Sebastian S, Takayama K, Hsu WT, Schultz RA, Neely K, Bryant M, Bulun SE (2003) Estrogen excess associated with novel gain-of-function mutations affecting the aromatase gene. N Engl J Med 348(19):1855–1865. https://doi.org/10.1056/NEJMoa021559
22. Sansone A, Romanelli F, Sansone M, Lenzi A, Di Luigi L (2017) Gynecomastia and hormones. Endocrine 55(1):37–44. https://doi.org/10.1007/s12020-016-0975-9
23. Rochefort H, Garcia M (1983) The estrogenic and antiestrogenic activities of androgens in female target tissues. Pharmacol Ther 23(2):193–216. https://doi.org/10.1016/0163-7258(83)90013-x
24. Isidori AM, Aversa A, Calogero A, Ferlin A, Francavilla S, Lanfranco F, Pivonello R, Rochira V, Corona G, Maggi M (2022) Adult- and late-onset male hypogonadism: the clinical practice guidelines of the Italian Society of Andrology and Sexual Medicine (SIAMS) and the Italian Society of Endocrinology (SIE). J Endocrinol Invest 45(12):2385–2403. https://doi.org/10.1007/s40618-022-01859-7
25. Bonomi M, Rochira V, Pasquali D, Balercia G, Jannini EA, Ferlin A, Klinefelter Italia NG (2017) Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. J Endocrinol Invest 40(2):123–134. https://doi.org/10.1007/s40618-016-0541-6
26. Calogero AE, Giagulli VA, Mongioi LM, Triggiani V, Radicioni AF, Jannini EA, Pasquali D, Klinefelter Italia NG (2017) Klinefelter syndrome: cardiovascular abnormalities and metabolic disorders. J Endocrinol Invest 40(7):705–712. https://doi.org/10.1007/s40618-017-0619-9
27. Ferlin A, Selice R, Angelini S, Di Grazia M, Caretta N, Cavalieri F, Di Mambro A, Foresta C (2018) Endocrine and psychological aspects of sexual dysfunction in Klinefelter patients. Andrology 6(3):414–419. https://doi.org/10.1111/andr.12474
28. Lee SW, Kwak DS, Jung IS, Kwak JH, Park JH, Hong SM, Lee CB, Park YS, Kim DS, Choi WH, Ahn YH (2015) Partial Androgen Insensitivity Syndrome Presenting with Gynecomastia. Endocrinol Metab (Seoul) 30(2):226–230. https://doi.org/10.3803/EnM.2015.30.2.226
29. Vaidyanathan P, Kaplowitz P (2018) Partial androgen insensitivity syndrome presenting as pubertal gynecomastia: clinical and hormonal findings and a novel mutation in the androgen receptor gene. Endocrinol Diabetes Metab Case Rep 2018. https://doi.org/10.1530/EDM-18-0128
30. Zinn AR, Ramos P, Elder FF, Kowal K, Samango-Sprouse C, Ross JL (2005) Androgen receptor CAGn repeat length influences phenotype of 47,XXY (Klinefelter) syndrome. J Clin Endocrinol Metab 90(9):5041–5046. https://doi.org/10.1210/jc.2005-0432

31. Karaayvaz S (2019) Clinical Evaluation of Breast in Childhood. Eur J Breast Health 15(3):137–140. https://doi.org/10.5152/ejbh.2019.4745
32. Ayyavoo A (2023) Gynecomastia. Indian J Pediatr 90(10):1013–1017. https://doi.org/10.1007/s12098-023-04810-7
33. Sloand E (1998) Pediatric and adolescent breast health. Lippincotts Prim Care Pract 2(2):170–175
34. McKiernan JF, Hull D (1981) Breast development in the newborn. Arch Dis Child 56(7):525–529. https://doi.org/10.1136/adc.56.7.525
35. Ferreira M, Mesquita M, Quaresma M, Andre S (2008) Prolactin receptor expression in gynaecomastia and male breast carcinoma. Histopathology 53(1):56–61. https://doi.org/10.1111/j.1365-2559.2008.03059.x
36. Hovey RC, Trott JF, Ginsburg E, Goldhar A, Sasaki MM, Fountain SJ, Sundararajan K, Vonderhaar BK (2001) Transcriptional and spatiotemporal regulation of prolactin receptor mRNA and cooperativity with progesterone receptor function during ductal branch growth in the mammary gland. Dev Dyn 222(2):192–205. https://doi.org/10.1002/dvdy.1179
37. Mertani HC, Garcia-Caballero T, Lambert A, Gerard F, Palayer C, Boutin JM, Vonderhaar BK, Waters MJ, Lobie PE, Morel G (1998) Cellular expression of growth hormone and prolactin receptors in human breast disorders. Int J Cancer 79(2):202–211. https://doi.org/10.1002/(sici)1097-0215(19980417)79:2%3C202::aid-ijc17%3E3.0.co;2-b
38. Harvey PW, Everett DJ, Springall CJ (2006) Hyperprolactinaemia as an adverse effect in regulatory and clinical toxicology: role in breast and prostate cancer. Hum Exp Toxicol 25(7):395–404. https://doi.org/10.1191/0960327106ht643oa
39. Schmidt IM, Chellakooty M, Haavisto AM, Boisen KA, Damgaard IN, Steendahl U, Toppari J, Skakkebaek NE, Main KM (2002) Gender difference in breast tissue size in infancy: correlation with serum estradiol. Pediatr Res 52(5):682–686. https://doi.org/10.1203/00006450-200211000-00012
40. Walden PD, Ruan W, Feldman M, Kleinberg DL (1998) Evidence that the mammary fat pad mediates the action of growth hormone in mammary gland development. Endocrinology 139(2):659–662. https://doi.org/10.1210/endo.139.2.5718
41. Tenuta M, Carlomagno F, Cangiano B, Kanakis G, Pozza C, Sbardella E, Isidori AM, Krausz C, Gianfrilli D (2021) Somatotropic-Testicular Axis: A crosstalk between GH/IGF-I and gonadal hormones during development, transition, and adult age. Andrology 9(1):168–184. https://doi.org/10.1111/andr.12918
42. Mieritz MG, Raket LL, Hagen CP, Nielsen JE, Talman ML, Petersen JH, Sommer SH, Main KM, Jorgensen N, Juul A (2015) A Longitudinal Study of Growth, Sex Steroids, and IGF-1 in Boys With Physiological Gynecomastia. J Clin Endocrinol Metab 100(10):3752–3759. https://doi.org/10.1210/jc.2015-2836
43. Kleinberg DL, Feldman M, Ruan W (2000) IGF-I: an essential factor in terminal end bud formation and ductal morphogenesis. J Mammary Gland Biol Neoplasia 5(1):7–17. https://doi.org/10.1023/a:1009507030633
44. Pinelli M, De Maria F, Ceccarelli P, Pedrieri B, Bianchini MA, Iughetti L, De Santis G (2023) Gynecomastia: an uncommon, destabilizing condition of the male adolescent. our therapeutic choice. Acta Biomed 94(2):e2023055. https://doi.org/10.23750/abm.v94i2.14028
45. Dickson G (2012) Gynecomastia. Am Fam Physician 85(7):716–722
46. Lashin R, Youssef RA, Elshahat A, Mohamed EN (2023) Postoperative Psychological Impact on Teenagers after Gynecomastia Correction. Plast Reconstr Surg Glob Open 11(6):e5094. https://doi.org/10.1097/GOX.0000000000005094
47. Braunstein GD (1999) Aromatase and gynecomastia. Endocr Relat Cancer 6(2):315–324. https://doi.org/10.1677/erc.0.0060315
48. Eckman A, Dobs A (2008) Drug-induced gynecomastia. Expert Opin Drug Saf 7(6):691–702. https://doi.org/10.1517/14740330802442382
49. Satoh T, Munakata H, Fujita K, Itoh S, Itoh S, Kamataki T, Yoshizawa I (2003) Studies on the interactions between drug and estrogen. II. On the inhibitory effect of 29 drugs reported to induce gynecomastia on the oxidation of estradiol at C-2 or C-17. Biol Pharm Bull 26(5):695–700. https://doi.org/10.1248/bpb.26.695
50. Trump DL, Pavy MD, Staal S (1982) Gynecomastia in men following antineoplastic therapy. Arch Intern Med 142(3):511–513
51. Krause W (2012) Drug-inducing gynaecomastia–a critical review. Andrologia. 44 Suppl 1621 – 626. https://doi.org/10.1111/j.1439-0272.2011.01240.x
52. Forest MG, Lecoq A, Saez JM (1979) Kinetics of human chorionic gonadotropin-induced steroidogenic response of the human testis. II. Plasma 17 alpha-hydroxyprogesterone, delta4-androstenedione, estrone, and 17 beta-estradiol: evidence for the action of human chorionic gonadotropin on intermediate enzymes implicated in steroid biosynthesis. J Clin Endocrinol Metab 49(2):284–291. https://doi.org/10.1210/jcem-49-2-284
53. Pozza C, Kanakis G, Carlomagno F, Lemma A, Pofi R, Tenuta M, Minnetti M, Tarsitano MG, Sesti F, Paoli D, Anzuini A, Lenzi A, Isidori AM, Gianfrilli D (2020) Testicular ultrasound score: A new proposal for a scoring system to predict testicular function. Andrology 8(5):1051–1063. https://doi.org/10.1111/andr.12822
54. Pozza C, Sesti F, Tenuta M, Spaziani M, Tarantino C, Carlomagno F, Minnetti M, Pofi R, Paparella R, Lenzi A, Radicioni A, Isidori AM, Tarani L, Gianfrilli D (2023) Testicular Dysfunction in 47,XXY Boys: When It All Begins. A Semilongitudinal Study. J Clin Endocrinol Metab 108(10):2486–2499. https://doi.org/10.1210/clinem/dgad205
55. Bellastella G, Menafra D, Puliani G, Colao A, Savastano S, Obesity Programs of nutrition ER, Assessment G (2019) How much does obesity affect the male reproductive function? Int J Obes Suppl. 9(1):50–64. https://doi.org/10.1038/s41367-019-0008-2
56. Pivonello R, Menafra D, Riccio E, Garifalos F, Mazzella M, de Angelis C, Colao A (2019) Metabolic Disorders and Male Hypogonadotropic Hypogonadism. Front Endocrinol (Lausanne). 10345. https://doi.org/10.3389/fendo.2019.00345
57. Grossmann M, Matsumoto AM (2017) A Perspective on Middle-Aged and Older Men With Functional Hypogonadism: Focus on Holistic Management. J Clin Endocrinol Metab 102(3):1067–1075. https://doi.org/10.1210/jc.2016-3580
58. Corona G, Rastrelli G, Monami M, Saad F, Luconi M, Lucchese M, Facchiano E, Sforza A, Forti G, Mannucci E, Maggi M (2013) Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. Eur J Endocrinol 168(6):829–843. https://doi.org/10.1530/EJE-12-0955
59. Wake DJ, Strand M, Rask E, Westerbacka J, Livingstone DE, Soderberg S, Andrew R, Yki-Jarvinen H, Olsson T, Walker BR (2007) Intra-adipose sex steroid metabolism and body fat distribution in idiopathic human obesity. Clin Endocrinol (Oxf) 66(3):440–446. https://doi.org/10.1111/j.1365-2265.2007.02755.x
60. Hassan HC, Cullen IM, Casey RG, Rogers E (2008) Gynaecomastia: an endocrine manifestation of testicular cancer. Andrologia 40(3):152–157. https://doi.org/10.1111/j.1439-0272.2007.00815.x
61. Carmignani L, Salvioni R, Gadda F, Colecchia M, Gazzano G, Torelli T, Rocco F, Colpi GM, Pizzocaro G (2006) Long-term followup and clinical characteristics of testicular Leydig cell tumor: experience with 24 cases. J Urol 176(5):2040–2043 discussion 2043. https://doi.org/10.1016/j.juro.2006.07.005
62. Pozza C, Pofi R, Tenuta M, Tarsitano MG, Sbardella E, Fattorini G, Cantisani V, Lenzi A, Isidori AM, Gianfrilli D, Testis U (2019)

Clinical presentation, management and follow-up of 83 patients with Leydig cell tumors of the testis: a prospective case-cohort study. Hum Reprod 34(8):1389–1403. https://doi.org/10.1093/humrep/dez083
63. Polat AV, Ozturk M, Camlidag I, Akyuz B (2019) Is gynecomastia related to the disease characteristics and prognosis in testicular germ cell tumor patients? Diagn Interv Radiol 25(3):189–194. https://doi.org/10.5152/dir.2019.18297
64. Hernes EH, Harstad K, Fossa (1996) Changing incidence and delay of testicular cancer in southern Norway (1981–1992). Eur Urol 30(3):349–357. https://doi.org/10.1159/000474195
65. Meikle AW (2004) The interrelationships between thyroid dysfunction and hypogonadism in men and boys. Thyroid. 14 Suppl 1S17-25. https://doi.org/10.1089/105072504323024552
66. Ho HK, Loh KC (1998) Hyperthyroidism with gynaecomastia as the initial complaint: a case report. Ann Acad Med Singap 27(4):594–596
67. Young DB (2015) 6'6 United States Marine Seeks Treatment for Gynecomastia Only to Learn It Is All in His Head. Mil Med 180(12):e1290–1292. https://doi.org/10.7205/MILMED-D-15-00248
68. Reinehr T, Kulle A, Barth A, Ackermann J, Lass N, Holterhus PM (2020) Sex Hormone Profile in Pubertal Boys With Gynecomastia and Pseudogynecomastia. J Clin Endocrinol Metab 105(4). https://doi.org/10.1210/clinem/dgaa044
69. Volm MD, Talamonti MS, Thangavelu M, Gradishar WK (1997) Pituitary adenoma and bilateral male breast cancer: an unusual association. J Surg Oncol 64(1):74–78. https://doi.org/10.1002/(sici)1096-9098(199701)64:1%3C74::aid-jso14%3E3.0.co;2-w
70. Fentiman IS, Fourquet A, Hortobagyi GN (2006) Male breast cancer. Lancet 367(9510):595–604. https://doi.org/10.1016/S0140-6736(06)68226-3
71. Chung EY, Ruospo M, Natale P, Bolignano D, Navaneethan SD, Palmer SC, Strippoli GF (2020) Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of chronic kidney disease. Cochrane Database Syst Rev 10(10):CD007004. https://doi.org/10.1002/14651858.CD007004.pub4
72. Iglesias P, Carrero JJ, Diez JJ (2012) Gonadal dysfunction in men with chronic kidney disease: clinical features, prognostic implications and therapeutic options. J Nephrol 25(1):31–42. https://doi.org/10.5301/JN.2011.8481
73. Mira JA, Lozano F, Santos J, Ramayo E, Terron A, Palacios R, Leon EM, Marquez M, Macias J, Fernandez-Palacin A, Gomez-Mateos J, Pineda JA Grupo Andaluz para el Estudio de las Enfermedades I (2004) Gynaecomastia in HIV-infected men on highly active antiretroviral therapy: association with efavirenz and didanosine treatment. Antivir Ther 9(4):511–517.
74. Zifroni A, Schiavi RC, Schaffner F (1991) Sexual function and testosterone levels in men with nonalcoholic liver disease. Hepatology 14(3):479–482
75. Sinclair M, Grossmann M, Gow PJ, Angus PW (2015) Testosterone in men with advanced liver disease: abnormalities and implications. J Gastroenterol Hepatol 30(2):244–251. https://doi.org/10.1111/jgh.12695
76. Brauner EV, Uldbjerg C, Lim YH, Beck A, Hueg T, Juul A (2024) Is male gynaecomastia associated with an increased risk of death? A nationwide register-based cohort study. BMJ Open 14(2):e076608. https://doi.org/10.1136/bmjopen-2023-076608
77. Garcia-Benayas T, Blanco F, Martin-Carbonero L, Valencia E, Barrios A, Gonzalez-Lahoz J, Soriano V (2003) Gynecomastia in HIV-infected patients receiving antiretroviral therapy. AIDS Res Hum Retroviruses 19(9):739–741. https://doi.org/10.1089/088922203769232539
78. Osman S, Mansoor E, Buccimazza I (2020) Gynaecomastia in the Durban Breast Unit: A Comparison of HIV- and Non-HIV-Infected Individuals. World J Surg 44(5):1538–1546. https://doi.org/10.1007/s00268-019-05350-y
79. Manfredi R, Calza L, Chiodo F (2004) Another emerging event occurring during HIV infection treated with any antiretroviral therapy: frequency and role of gynecomastia. Infez Med 12(1):51–59
80. Piroth LGM, Petit JM, Buisson M, Duong M, Chavanet P, Portier H (2001) Incidence of gynecomastia in men infected with HIV and treated with highly active antiretroviral therapy. Scand J Infect Dis 33(7):559–560. https://doi.org/10.1080/00365540110026476
81. De Vincentis S, Rochira V (2023) Update on acquired hypogonadism in men living with HIV: pathogenesis, clinic, and treatment. Front Endocrinol (Lausanne) 141201696. https://doi.org/10.3389/fendo.2023.1201696
82. Barzon L, Zamboni M, Pacenti M, Milan G, Bosello O, Federspil G, Palu G, Vettor R (2005) Do oestrogen receptors play a role in the pathogenesis of HIV-associated lipodystrophy? AIDS 19(5):531–533. https://doi.org/10.1097/01.aids.0000162344.73804.a1
83. Essafi MA, Elazizi L, Aynaou H, Salhi H, El Ouahabi H (2022) Reversible Gynecomastia in HIV-Infected Man Treated With Triple Antiretroviral Therapy Containing Efavirenz: A Case Report. Cureus 14(8):e27991. https://doi.org/10.7759/cureus.27991
84. Manfredi R, Calza L, Chiodo F (2004) Gynecomastia, lipodystrophy syndrome, and dyslipidemia occurring or worsening during antiretroviral regimens other than protease inhibitor-based ones. J Acquir Immune Defic Syndr 35(1):99–102. https://doi.org/10.1097/00126334-200401010-00017
85. Allen EAPA, Siddiqui MT, Clark DP, Ali SZ (2003) Cytopathologic findings in breast masses in men with HIV infection. Acta Cytol 47(2):5. https://doi.org/10.1159/000326501
86. Coyne JD (2016) Gynecomastia With Atypical Ductal Hyperplasia and Ductal Carcinoma In Situ Associated With Invasive Breast Carcinoma in a Male Patient on Antiretroviral Therapy: A Case Report. Int J Surg Pathol 24(2):139–141. https://doi.org/10.1177/1066896915608437
87. Benveniste O, Simon A, Herson S (2001) Successful percutaneous dihydrotestosterone treatment of gynecomastia occurring during highly active antiretroviral therapy: four cases and a review of the literature. Clin Infect Dis 33(6):891–893. https://doi.org/10.1086/322637
88. Kegg S, Lau R (2002) Tamoxifen in antiretroviral-associated gynaecomastia. Int J STD AIDS 13(8):582–583. https://doi.org/10.1258/095646202760159756
89. Uldbjerg CS, Lim YH, Brauner EV, Juul A (2023) Increased Morbidity in Males Diagnosed With Gynecomastia: A Nationwide Register-based Cohort Study. J Clin Endocrinol Metab 108(7):e380–e387. https://doi.org/10.1210/clinem/dgad048
90. Iturriaga H, Lioi X, Valladares L (1999) Sex hormone-binding globulin in non-cirrhotic alcoholic patients during early withdrawal and after longer abstinence. Alcohol Alcohol 34(6):903–909. https://doi.org/10.1093/alcalc/34.6.903
91. Emanuele MA, Emanuele NV (1998) Alcohol's effects on male reproduction. Alcohol Health Res World 22(3):195–201
92. Deepinder F, Braunstein GD (2012) Drug-induced gynecomastia: an evidence-based review. Expert Opin Drug Saf 11(5):779–795. https://doi.org/10.1517/14740338.2012.712109
93. Murtha L, Sathiadoss P, Salameh JP, McInnes MDF, Revah G (2023) Chest CT Findings in Marijuana Smokers. Radiology 307(1):e212611. https://doi.org/10.1148/radiol.212611
94. Braunstein GD (2023) Causal Relationship between Smoking Marijuana and Gynecomastia Remains Unproven. Radiology 307(5):e223046. https://doi.org/10.1148/radiol.223046
95. Rochira V, Carani C (2000) Estrogens, Male Reproduction and Beyond. In: *Endotext.* edn. Edited by Feingold KR, Ahmed SF, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K South Dartmouth (MA)

96. Fukami M, Ogata T (2022) Congenital disorders of estrogen biosynthesis and action. Best Pract Res Clin Endocrinol Metab 36(1):101580. https://doi.org/10.1016/j.beem.2021.101580
97. Patjamontri S, Lucas-Herald AK, Bryce J, van den Akker E, Cools M, Globa E, Guerra-Junior G, Hiort O, Hofman P, Holterhus PM, Hughes IA, Juul A, Nordenstrom A, Russo G, Stancampiano MR, Seneviratne SN, Tadokoro-Cuccaro R, Thankamony A, Weintrob N, Zelinska N, Ahmed SF (2025) Gynecomastia and Its Management In Boys With Partial Androgen Insensitivity Syndrome. J Clin Endocrinol Metab. 110(6):e2018-e2025. https://doi.org/10.1210/clinem/dgae562
98. Dejager S, Bry-Gauillard H, Bruckert E, Eymard B, Salachas F, LeGuern E, Tardieu S, Chadarevian R, Giral P, Turpin G (2002) A comprehensive endocrine description of Kennedy's disease revealing androgen insensitivity linked to CAG repeat length. J Clin Endocrinol Metab 87(8):3893–3901. https://doi.org/10.1210/jcem.87.8.8780
99. Skafida M, Duvall MM, Zelley K, Baldino SE, Brodeur GM, Kolon T, Mostoufi-Moab S, MacFarland SP (2024) Conservative management of gynecomastia in Peutz-Jeghers syndrome: Case series and review of the literature. Pediatr Blood Cancer 71(10):e31180. https://doi.org/10.1002/pbc.31180
100. Alruwaili TK, Alkanhal KI, AlShoomi AM, Almanie DA, Alahmed MH (2022) A 14-Year-Old Saudi Boy with Gynecomastia, Cushing Syndrome, Large-Cell Calcifying Sertoli Cell Tumor of the Testis, and Carney Complex. Am J Case Rep 23e937404. https://doi.org/10.12659/AJCR.937404
101. Tacheci I, Kopacova M, Bures J (2021) Peutz-Jeghers syndrome. Curr Opin Gastroenterol 37(3):245–254. https://doi.org/10.1097/MOG.0000000000000718
102. Stratakis CA (1993) Carney Complex. In: *GeneReviews((R)).* edn. Edited by Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A. Seattle (WA)
103. Wasniewska M, Raiola G, Galati MC, Salzano G, Rulli I, Zirilli G, De Luca F (2008) Non-classical 21-hydroxylase deficiency in boys with prepubertal or pubertal gynecomastia. Eur J Pediatr 167(9):1083–1084. https://doi.org/10.1007/s00431-007-0625-6
104. Auchterlonie IA, Cameron J, Wallace AM, Rudd BT, Hudson M, Smail PJ (1985) Pre-pubertal gynaecomastia as the presenting feature of late-onset 21-hydroxylase deficiency. Horm Res 22(1–2):94–99. https://doi.org/10.1159/000180079
105. Blackett MP, Freeman MD (1996) Androstenedione aromatization as a cause of gynecomastia in 11beta-hydroxylase and 21-hydroxylase deficiencies. Endocr Pract 2(2):90–93. https://doi.org/10.4158/EP.2.2.90
106. Bonomi M, Cangiano B, Cianfarani S, Garolla A, Gianfrilli D, Lanfranco F, Rastrelli G, Sbardella E, Corona G, Isidori AM, Rochira V (2025) Management of andrological disorders from childhood and adolescence to transition age: guidelines from the Italian Society of Andrology and Sexual Medicine (SIAMS) in collaboration with the Italian Society for Pediatric Endocrinology and Diabetology (SIEDP)-Part-1. J Endocrinol Invest 48(1):1–22. https://doi.org/10.1007/s40618-024-02435-x
107. Wisniewski AB, Batista RL, Costa EMF, Finlayson C, Sircili MHP, Denes FT, Domenice S, Mendonca BB (2019) Management of 46,XY Differences/Disorders of Sex Development (DSD) Throughout Life. Endocr Rev 40(6):1547–1572. https://doi.org/10.1210/er.2019-00049
108. Binder G, Nakamura A, Schweizer R, Ogata T, Fukami M, Nagasaki K (2021) Long-term Effect of Aromatase Inhibition in Aromatase Excess Syndrome. J Clin Endocrinol Metab 106(5):1491–1500. https://doi.org/10.1210/clinem/dgab054
109. Cools MNA, Robeva R, Hall J, Westerveld P, Flück C, Köhler B, Berra MSA, Schweizer K, Pasterski V (2018) COST Action BM1303 working group. Consensus Statement Nat Rev Endocrinol 14(7):14. https://doi.org/10.1038/s41574-018-0010-8
110. Sea JL, Abramyan M, Chiu HK (2021) Prepubescent unilateral gynecomastia secondary to excessive soy consumption. J Pediatr Endocrinol Metab 34(4):521–525. https://doi.org/10.1515/jpem-2020-0397
111. Takenaka T, Nagano M, Yamashita K, Kikuchi K (2020) Flaxseed oil stimulates gynecomastia. BMJ Case Rep 13(12). https://doi.org/10.1136/bcr-2020-237948
112. Corona G, Rastrelli G, Dicuio M, Concetti S, Minnetti M, Pivonello R, Isidori A, Sforza A, Maggi M (2021) Subclinical male hypogonadism. Minerva Endocrinol (Torino) 46(3):252–261. https://doi.org/10.23736/S2724-6507.20.03208-3
113. Rew L, Young C, Harrison T, Caridi R (2015) A systematic review of literature on psychosocial aspects of gynecomastia in adolescents and young men. J Adolesc 43206–43212. https://doi.org/10.1016/j.adolescence.2015.06.007
114. Puntis JW, Smith HL, Buick RG, Booth IW (1989) Effect of dystonic movements on oesophageal peristalsis in Sandifer's syndrome. Arch Dis Child 64(9):1311–1313. https://doi.org/10.1136/adc.64.9.1311
115. Iyngkaran N, Yadav M, Boey CG (1989) Rectal mucosa in cows' milk allergy. Arch Dis Child 64(9):1256–1260. https://doi.org/10.1136/adc.64.9.1256
116. Djaladat H, Nichols C, Daneshmand S (2011) Androgen-producing testicular germ cell tumors. J Clin Oncol 29(21):e634–635. https://doi.org/10.1200/JCO.2011.35.1965
117. Kaptanis S, Parvanta L, Beltran L (2014) Testicular seminoma presenting as unilateral gynecomastia. Breast J 20(4):424–426. https://doi.org/10.1111/tbj.12287
118. Vermeulen A, Verdonck L, Kaufman JM (1999) A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 84(10):3666–3672. https://doi.org/10.1210/jcem.84.10.6079
119. Huhtaniemi IT, Tajar A, Lee DM, O'Neill TW, Finn JD, Bartfai G, Boonen S, Casanueva FF, Giwercman A, Han TS, Kula K, Labrie F, Lean ME, Pendleton N, Punab M, Silman AJ, Vanderschueren D, Forti G, Wu FC, Group E (2012) Comparison of serum testosterone and estradiol measurements in 3174 European men using platform immunoassay and mass spectrometry; relevance for the diagnostics in aging men. Eur J Endocrinol 166(6):983–991. https://doi.org/10.1530/EJE-11-1051
120. Ohlsson C, Nilsson ME, Tivesten A, Ryberg H, Mellstrom D, Karlsson MK, Ljunggren O, Labrie F, Orwoll ES, Lee DM, Pye SR, O'Neill TW, Finn JD, Adams JE, Ward KA, Boonen S, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Huhtaniemi IT, Kula K, Lean ME, Pendleton N, Punab M, Vanderschueren D, Wu FC, Group ES, Vandenput L (2013) Comparisons of immunoassay and mass spectrometry measurements of serum estradiol levels and their influence on clinical association studies in men. J Clin Endocrinol Metab 98(6):E1097–1102. https://doi.org/10.1210/jc.2012-3861
121. Honour JW (2024) The interpretation of immunometric, chromatographic and mass spectrometric data for steroids in diagnosis of endocrine disorders. Steroids 211109502. https://doi.org/10.1016/j.steroids.2024.109502
122. Rosner W, Hankinson SE, Sluss PM, Vesper HW, Wierman ME (2013) Challenges to the measurement of estradiol: an endocrine society position statement. J Clin Endocrinol Metab 98(4):1376–1387. https://doi.org/10.1210/jc.2012-3780
123. Vesper HW, Botelho JC, Vidal ML, Rahmani Y, Thienpont LM, Caudill SP (2014) High variability in serum estradiol measurements in men and women. Steroids. 827 – 13. https://doi.org/10.1016/j.steroids.2013.12.005
124. Giannetta E, Gianfrilli D, Barbagallo F, Isidori AM, Lenzi A (2012) Subclinical male hypogonadism. Best Pract Res Clin Endocrinol Metab 26(4):539–550. https://doi.org/10.1016/j.beem.2011.12.005

125. Rajpert-De Meyts E, Aksglaede L, Bandak M, Toppari J, Jorgensen N (2000) Testicular Cancer: Pathogenesis, Diagnosis and Management with Focus on Endocrine Aspects. In: *Endotext.* edn. Edited by Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J South Dartmouth (MA)
126. Sanford DI, Asanad K, Nassiri N, Nabhani J (2022) Hyperandrogenism and Hyperestrogenism Secondary to Mixed Germ-Cell Testicular Tumor. Cureus 14(7):e27396. https://doi.org/10.7759/cureus.27396
127. Tenuta M, Sesti F, Bonaventura I, Mazzotta P, Pofi R, Gianfrilli D, Pozza C (2021) Use of contrast enhanced ultrasound in testicular diseases: A comprehensive review. Andrology 9(5):1369–1382. https://doi.org/10.1111/andr.13057
128. Expert Panel on, Breast I, Niell BL, Lourenco AP, Moy L, Baron P, Didwania AD, diFlorio-Alexander RM, Heller SL, Holbrook AI, Le-Petross HT, Lewin AA, Mehta TS, Slanetz PJ, Stuckey AR, Tuscano DS, Ulaner GA, Vincoff NS, Weinstein SP, Newell MS (2018) ACR Appropriateness Criteria((R)) Evaluation of the Symptomatic Male Breast. J Am Coll Radiol 15(11S):S313–S320. https://doi.org/10.1016/j.jacr.2018.09.017
129. Munoz Carrasco R, Alvarez Benito M, Munoz Gomariz E, Raya Povedano JL, Martinez Paredes M (2010) Mammography and ultrasound in the evaluation of male breast disease. Eur Radiol 20(12):2797–2805. https://doi.org/10.1007/s00330-010-1867-7
130. Hanavadi S, Monypenny IJ, Mansel RE (2006) Is mammography overused in male patients? Breast 15(1):123–126. https://doi.org/10.1016/j.breast.2005.02.005
131. Hines SL, Tan WW, Yasrebi M, DePeri ER, Perez EA (2007) The role of mammography in male patients with breast symptoms. Mayo Clin Proc. 82(3):297–300. https://doi.org/10.4065/82.3.297
132. Onder O, Azizova A, Durhan G, Elibol FD, Akpinar MG, Demirkazik F (2020) Imaging findings and classification of the common and uncommon male breast diseases. Insights Imaging 11(1):27. https://doi.org/10.1186/s13244-019-0834-3
133. Mathew J, Perkins GH, Stephens T, Middleton LP, Yang WT (2008) Primary breast cancer in men: clinical, imaging, and pathologic findings in 57 patients. AJR Am J Roentgenol 191(6):1631–1639. https://doi.org/10.2214/AJR.08.1076
134. Morrogh M, King TA (2009) The significance of nipple discharge of the male breast. Breast J 15(6):632–638. https://doi.org/10.1111/j.1524-4741.2009.00818.x
135. Munoz Carrasco R, Alvarez Benito M, Rivin del Campo E (2013) Value of mammography and breast ultrasound in male patients with nipple discharge. Eur J Radiol 82(3):478–484. https://doi.org/10.1016/j.ejrad.2012.10.019
136. Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN (2004) Breast carcinoma in men: a population-based study. Cancer 101(1):51–57. https://doi.org/10.1002/cncr.20312
137. Chau A, Jafarian N, Rosa M (2016) Male Breast: Clinical and Imaging Evaluations of Benign and Malignant Entities with Histologic Correlation. Am J Med 129(8):776–791. https://doi.org/10.1016/j.amjmed.2016.01.009
138. Patterson SK, Helvie MA, Aziz K, Nees AV (2006) Outcome of men presenting with clinical breast problems: the role of mammography and ultrasound. Breast J 12(5):418–423. https://doi.org/10.1111/j.1075-122X.2006.00298.x
139. Lotti F, Bertolotto M, Maggi M (2021) Historical trends for the standards in scrotal ultrasonography: What was, what is and what will be normal. Andrology 9(5):1331–1355. https://doi.org/10.1111/andr.13062
140. Greif JM, Pezzi CM, Klimberg VS, Bailey L, Zuraek M (2012) Gender differences in breast cancer: analysis of 13,000 breast cancers in men from the National Cancer Data Base. Ann Surg Oncol 19(10):3199–3204. https://doi.org/10.1245/s10434-012-2479-z
141. Kanakis GA, Nieschlag E (2018) Klinefelter syndrome: more than hypogonadism. Metabolism 86135–86144. https://doi.org/10.1016/j.metabol.2017.09.017
142. Radicioni AF, Ferlin A, Balercia G, Pasquali D, Vignozzi L, Maggi M, Foresta C, Lenzi A (2010) Consensus statement on diagnosis and clinical management of Klinefelter syndrome. J Endocrinol Invest 33(11):839–850. https://doi.org/10.1007/BF03350351
143. Sasco AJ, Lowenfels AB, Pasker-de Jong P (1993) Review article: epidemiology of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiological factors. Int J Cancer 53(4):538–549. https://doi.org/10.1002/ijc.2910530403
144. Swerdlow AJ, Schoemaker MJ, Higgins CD, Wright AF, Jacobs PA, Group UKCC (2005) Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. J Natl Cancer Inst 97(16):1204–1210. https://doi.org/10.1093/jnci/dji240
145. Brinton LA, Cook MB, McCormack V, Johnson KC, Olsson H, Casagrande JT, Cooke R, Falk RT, Gapstur SM, Gaudet MM, Gaziano JM, Gkiokas G, Guenel P, Henderson BE, Hollenbeck A, Hsing AW, Kolonel LN, Isaacs C, Lubin JH, Michels KB, Negri E, Parisi D, Petridou ET, Pike MC, Riboli E, Sesso HD, Snyder K, Swerdlow AJ, European Rare Cancer, Study G, Trichopoulos D, Ursin G, van den Brandt PA, Van Den Eeden SK, Weiderpass E, Willett WC, Ewertz M, Thomas DB (2014) Anthropometric and hormonal risk factors for male breast cancer: male breast cancer pooling project results. J Natl Cancer Inst 106(3):djt465. https://doi.org/10.1093/jnci/djt465
146. Billa E, Kanakis GA, Goulis DG (2021) Imaging in gynecomastia. Andrology 9(5):1444–1456. https://doi.org/10.1111/andr.13051
147. Dialani V, Baum J, Mehta TS (2010) Sonographic features of gynecomastia. J Ultrasound Med 29(4):539–547. https://doi.org/10.7863/jum.2010.29.4.539
148. Pozza C, Tenuta M, Sesti F, Bertolotto M, Huang DY, Sidhu PS, Maggi M, Isidori AM, Lotti F (2023) Multiparametric Ultrasound for Diagnosing Testicular Lesions: Everything You Need to Know in Daily Clinical Practice. Cancers (Basel) 15(22). https://doi.org/10.3390/cancers15225332
149. Janes SE, Lengyel JA, Singh S, Aluwihare N, Isgar B (2006) Needle core biopsy for the assessment of unilateral breast masses in men. Breast 15(2):273–275. https://doi.org/10.1016/j.breast.2005.05.003
150. Ferzoco RM, Ruddy KJ (2016) The Epidemiology of Male Breast Cancer. Curr Oncol Rep 18(1):1. https://doi.org/10.1007/s11912-015-0487-4
151. Bicchierai G, Nori J, Livi L, De Benedetto D, Vanzi E, Boeri C, Bianchi S, Becherini C, Meattini I (2017) Core needle biopsy for the assessment of unilateral male breast lesions. Eur J Surg Oncol 43(4):680–682. https://doi.org/10.1016/j.ejso.2016.07.144
152. Westenend PJ, Jobse C (2002) Evaluation of fine-needle aspiration cytology of breast masses in males. Cancer 96(2):101–104. https://doi.org/10.1002/cncr.10483
153. Siddiqui MT, Zakowski MF, Ashfaq R, Ali SZ (2002) Breast masses in males: multi-institutional experience on fine-needle aspiration. Diagn Cytopathol 26(2):87–91. https://doi.org/10.1002/dc.10066
154. Lazala C, Saenger P (2002) Pubertal gynecomastia. J Pediatr Endocrinol Metab 15(5):553–560. https://doi.org/10.1515/jpem.2002.15.5.553
155. Nydick M, Bustos J, Dale JH Jr., Rawson RW (1961) Gynecomastia in adolescent boys. JAMA 178449–178454. https://doi.org/10.1001/jama.1961.03040440001001
156. Lee PA (1975) The relationship of concentrations of serum hormones to pubertal gynecomastia. J Pediatr 86(2):212–215. https://doi.org/10.1016/s0022-3476(75)80470-7

157. Biro FM, Lucky AW, Huster GA, Morrison JA (1990) Hormonal studies and physical maturation in adolescent gynecomastia. J Pediatr 116(3):450–455. https://doi.org/10.1016/s0022-3476(05)82843-4
158. Schanz S, Schreiber G, Zitzmann M, Krapohl BD, Horch R, Kohn FM (2017) S1 guidelines: Gynecomastia in adults. J Dtsch Dermatol Ges 15(4):465–472. https://doi.org/10.1111/ddg.13080
159. Bulard J, Mowszowicz I, Schaison G (1987) Increased aromatase activity in pubic skin fibroblasts from patients with isolated gynecomastia. J Clin Endocrinol Metab 64(3):618–623. https://doi.org/10.1210/jcem-64-3-618
160. Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA (1999) Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. J Clin Endocrinol Metab 84(10):3469–3478. https://doi.org/10.1210/jcem.84.10.6078
161. Kuhn JM, Roca R, Laudat MH, Rieu M, Luton JP, Bricaire H (1983) Studies on the treatment of idiopathic gynaecomastia with percutaneous dihydrotestosterone. Clin Endocrinol (Oxf) 19(4):513–520. https://doi.org/10.1111/j.1365-2265.1983.tb00026.x
162. Eberle AJ, Sparrow JT, Keenan BS (1986) Treatment of persistent pubertal gynecomastia with dihydrotestosterone heptanoate. J Pediatr 109(1):144–149. https://doi.org/10.1016/s0022-3476(86)80596-0
163. Ting AC, Chow LW, Leung YF (2000) Comparison of tamoxifen with danazol in the management of idiopathic gynecomastia. Am Surg 66(1):38–40
164. Alagaratnam TT (1987) Idiopathic gynecomastia treated with tamoxifen: a preliminary report. Clin Ther 9(5):483–487
165. Derman O, Kanbur N, Kilic I, Kutluk T (2008) Long-term follow-up of tamoxifen treatment in adolescents with gynecomastia. J Pediatr Endocrinol Metab 21(5):449–454. https://doi.org/10.1515/jpem.2008.21.5.449
166. Khan HN, Rampaul R, Blamey RW (2004) Management of physiological gynaecomastia with tamoxifen. Breast 13(1):61–65. https://doi.org/10.1016/j.breast.2003.10.005
167. Stepanas AV, Burnet RB, Harding PE, Wise PH (1977) Clomiphene in the treatment of pubertal-adolescent gynecomastia: a preliminary report. J Pediatr 90(4):651–653. https://doi.org/10.1016/s0022-3476(77)80394-6
168. LeRoith D, Sobel R, Glick SM (1980) The effect of clomiphene citrate on pubertal gynaecomastia. Acta Endocrinol (Copenh) 95(2):177–180. https://doi.org/10.1530/acta.0.0950177
169. Plourde PV, Reiter EO, Jou HC, Desrochers PE, Rubin SD, Bercu BB, Diamond FB Jr., Backeljauw PF (2004) Safety and efficacy of anastrozole for the treatment of pubertal gynecomastia: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 89(9):4428–4433. https://doi.org/10.1210/jc.2004-0082
170. Buckle R (1979) Danazol therapy in gynaecomastia; recent experience and indications for therapy. Postgrad Med J 55(Suppl 571):78. doi:
171. Beck W, Stubbe P (1982) Endocrinological studies of the hypothalamo-pituitary gonadal axis during danazol treatment in pubertal boys with marked gynecomastia. Horm Metab Res 14(12):653–657. https://doi.org/10.1055/s-2007-1019110
172. Zachmann M, Eiholzer U, Muritano M, Werder EA, Manella B (1986) Treatment of pubertal gynaecomastia with testolactone. Acta Endocrinol Suppl (Copenh) 279218–279226. https://doi.org/10.1530/acta.0.112s218
173. Rhoden EL, Morgentaler A (2004) Treatment of testosterone-induced gynecomastia with the aromatase inhibitor, anastrozole. Int J Impot Res 16(1):95–97. https://doi.org/10.1038/sj.ijir.3901154
174. Mauras N, Bishop K, Merinbaum D, Emeribe U, Agbo F, Lowe E (2009) Pharmacokinetics and pharmacodynamics of anastrozole in pubertal boys with recent-onset gynecomastia. J Clin Endocrinol Metab 94(8):2975–2978. https://doi.org/10.1210/jc.2008-2527
175. Parker LN, Gray DR, Lai MK, Levin ER (1986) Treatment of gynecomastia with tamoxifen: a double-blind crossover study. Metabolism 35(8):705–708. https://doi.org/10.1016/0026-0495(86)90237-4
176. McDermott MT, Hofeldt FD, Kidd GS (1990) Tamoxifen therapy for painful idiopathic gynecomastia. South Med J 83(11):1283–1285. https://doi.org/10.1097/00007611-199011000-00013
177. Jones DJ, Holt SD, Surtees P, Davison DJ, Coptcoat MJ (1990) 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 72(5):296–298
178. Boccardo F, Rubagotti A, Battaglia M, Di Tonno P, Selvaggi FP, Conti G, Comeri G, Bertaccini A, Martorana G, Galassi P, Zattoni F, Macchiarella A, Siragusa A, Muscas G, Durand F, Potenzoni D, Manganelli A, Ferraris V, Montefiore F (2005) Evaluation of tamoxifen and anastrozole in the prevention of gynecomastia and breast pain induced by bicalutamide monotherapy of prostate cancer. J Clin Oncol 23(4):808–815. https://doi.org/10.1200/JCO.2005.12.013
179. Di Lorenzo G, Perdona S, De Placido S, D'Armiento M, Gallo A, Damiano R, Pingitore D, Gallo L, De Sio M, Autorino R (2005) Gynecomastia and breast pain induced by adjuvant therapy with bicalutamide after radical prostatectomy in patients with prostate cancer: the role of tamoxifen and radiotherapy. J Urol 174(6):2197–2203. https://doi.org/10.1097/01.ju.0000181824.28382.5c
180. Fradet Y, Egerdie B, Andersen M, Tammela TL, Nachabe M, Armstrong J, Morris T, Navani S (2007) Tamoxifen as prophylaxis for prevention of gynaecomastia and breast pain associated with bicalutamide 150 mg monotherapy in patients with prostate cancer: a randomised, placebo-controlled, dose-response study. Eur Urol 52(1):106–114. https://doi.org/10.1016/j.eururo.2007.01.031
181. Perdona S, Autorino R, De Placido S, D'Armiento M, Gallo A, Damiano R, Pingitore D, Gallo L, De Sio M, Bianco AR, Di Lorenzo G (2005) Efficacy of tamoxifen and radiotherapy for prevention and treatment of gynaecomastia and breast pain caused by bicalutamide in prostate cancer: a randomised controlled trial. Lancet Oncol 6(5):295–300. https://doi.org/10.1016/S1470-2045(05)70103-0
182. Saltzstein D, Sieber P, Morris T, Gallo J (2005) Prevention and management of bicalutamide-induced gynecomastia and breast pain: randomized endocrinologic and clinical studies with tamoxifen and anastrozole. Prostate Cancer Prostatic Dis 8(1):75–83. https://doi.org/10.1038/sj.pcan.4500782
183. Serretta V, Altieri V, Morgia G, Nicolosi F, De Grande G, Mazza R, Melloni D, Allegro R, Ferrau F, Gebbia V (2012) A randomized trial comparing tamoxifen therapy vs. tamoxifen prophylaxis in bicalutamide-induced gynecomastia. Clin Genitourin Cancer 10(3):174–179. https://doi.org/10.1016/j.clgc.2012.03.002
184. Widmark A, Fossa SD, Lundmo P, Damber JE, Vaage S, Damber L, Wiklund F, Klepp O (2003) Does prophylactic breast irradiation prevent antiandrogen-induced gynecomastia? Evaluation of 253 patients in the randomized Scandinavian trial SPCG-7/SFUO-3. Urology 61(1):145–151. https://doi.org/10.1016/s0090-4295(02)02107-6
185. Tyrrell CJ, Payne H, Tammela TL, Bakke A, Lodding P, Goedhals L, Van Erps P, Boon T, Van De Beek C, Andersson SO, Morris T, Carroll K (2004) Prophylactic breast irradiation with a single dose of electron beam radiotherapy (10 Gy) significantly reduces the incidence of bicalutamide-induced gynecomastia. Int J Radiat

Oncol Biol Phys 60(2):476–483. https://doi.org/10.1016/j.ijrobp.2004.03.022
186. Ozen H, Akyol F, Toktas G, Eskicorapci S, Unluer E, Kuyumcuoglu U, Abay E, Cureklibatur I, Sengoz M, Yalcin V, Akpinar H, Zorlu F, Sengor F, Karaman I (2010) Is prophylactic breast radiotherapy necessary in all patients with prostate cancer and gynecomastia and/or breast pain? J Urol 184(2):519–524. https://doi.org/10.1016/j.juro.2010.03.137
187. Berger O, Landau Z, Talisman R (2022) Gynecomastia: A systematic review of pharmacological treatments. Front Pediatr 10978311. https://doi.org/10.3389/fped.2022.978311
188. Canu L, Sparano C, Naletto L, De Filpo G, Cantini G, Rapizzi E, Martinelli S, Ercolino T, Cioppi F, Fantoni A, Zanatta L, Terreni A, Mannelli M, Luconi M, Maggi M, Lotti F (2023) Hypogonadism and sexual function in men affected by adrenocortical carcinoma under mitotane therapy. Front Endocrinol (Lausanne). 141320722. https://doi.org/10.3389/fendo.2023.1320722
189. Kuhn JM, Laudat MH, Roca R, Dugue MA, Luton JP, Bricaire H (1983) [Gynecomastia: effect of prolonged treatment with dihydrotestosterone by the percutaneous route]. Presse Med 12(1):21–25
190. Tsuboi I, Schulz RJ, Laukhtina E, Wada K, Karakiewicz PI, Araki M, Shariat SF (2025) Incidence, Management, and Prevention of Gynecomastia and Breast Pain in Patients with Prostate Cancer Undergoing Antiandrogen Therapy: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Eur Urol Open Sci 7331–7342. https://doi.org/10.1016/j.euros.2025.01.001
191. Spagnolo L, Tienforti D, Moretto C, Tonni C, Donatelli V, Ferranti A, Puocci G, Capuano C, Barbonetti A (2025) Prevention of bicalutamide-induced breast events in patients with prostate cancer: a meta-analysis of randomized controlled trials. J Endocrinol Invest doi. https://doi.org/10.1007/s40618-025-02583-8
192. Bedognetti D, Rubagotti A, Conti G, Francesca F, De Cobelli O, Canclini L, Gallucci M, Aragona F, Di Tonno P, Cortellini P, Martorana G, Lapini A, Boccardo F (2010) An open, randomised, multicentre, phase 3 trial comparing the efficacy of two tamoxifen schedules in preventing gynaecomastia induced by bicalutamide monotherapy in prostate cancer patients. Eur Urol 57(2):238–245. https://doi.org/10.1016/j.eururo.2009.05.019
193. Fischer S, Hirsch T, Hirche C, Kiefer J, Kueckelhaus M, Germann G, Reichenberger MA (2014) Surgical treatment of primary gynecomastia in children and adolescents. Pediatr Surg Int 30(6):641–647. https://doi.org/10.1007/s00383-014-3508-8
194. Daniels IR, Layer GT (2003) How should gynaecomastia be managed? ANZ J Surg 73(4):213–216. https://doi.org/10.1046/j.1445-1433.2002.02584.x
195. Daniels IR, Layer GT (2001) Gynaecomastia. Eur J Surg 167(12):885–892. https://doi.org/10.1080/110241501753361550
196. Mathur R, Braunstein GD (1997) Gynecomastia: pathomechanisms and treatment strategies. Horm Res 48(3):95–102. https://doi.org/10.1159/000185497
197. Fruhstorfer BH, Malata CM (2003) A systematic approach to the surgical treatment of gynaecomastia. Br J Plast Surg 56(3):237–246. https://doi.org/10.1016/s0007-1226(03)00111-5
198. Boljanovic S, Axelsson CK, Elberg JJ (2003) Surgical treatment of gynecomastia: liposuction combined with subcutaneous mastectomy. Scand J Surg 92(2):160–162. https://doi.org/10.1177/145749690309200209
199. Carlson HE (2011) Approach to the patient with gynecomastia. J Clin Endocrinol Metab 96(1):15–21. https://doi.org/10.1210/jcem.96.9.zeg15a
200. Ordaz DL, Thompson JK (2015) Gynecomastia and psychological functioning: A review of the literature. Body Image 15141–15148. https://doi.org/10.1016/j.bodyim.2015.08.004
201. Storch EA, Lewin AB, Geffken GR, Heidgerken AD, Stawser MS, Baumeister A, Silverstein JH (2004) Psychosocial adjustment of two boys with gynecomastia. J Paediatr Child Health 40(5–6):331. https://doi.org/10.1111/j.1440-1754.2004.00387.x
202. Schonfeld WA (1962) Gynecomastia in adolescence: effect on body image and personality adaptation. Psychosom Med 24379–24389. https://doi.org/10.1097/00006842-196200700-00008
203. Kinsella C Jr., Landfair A, Rottgers SA, Cray JJ, Weidman C, Deleyiannis FW, Grunwaldt L, Losee JE (2012) The psychological burden of idiopathic adolescent gynecomastia. Plast Reconstr Surg 129(1):1–7. https://doi.org/10.1097/PRS.0b013e3182361efd
204. Kasielska A, Antoszewski B (2011) Effect of operative treatment on psychosocial problems of men with gynaecomastia. Pol Przegl Chir 83(11):614–621. https://doi.org/10.2478/v10035-011-0097-2
205. Sollie M (2018) Management of gynecomastia-changes in psychological aspects after surgery-a systematic review. Gland Surg 7(Suppl 1):S70–S76. https://doi.org/10.21037/gs.2018.03.09
206. Wollina U, Goldman A (2011) Minimally invasive esthetic procedures of the male breast. J Cosmet Dermatol 10(2):150–155. https://doi.org/10.1111/j.1473-2165.2011.00548.x
207. Atiyeh B, Costagliola M, Illouz YG, Dibo S, Zgheib E, Rampillon F (2015) Functional and Therapeutic Indications of Liposuction: Personal Experience and Review of the Literature. Ann Plast Surg 75(2):231–245. https://doi.org/10.1097/SAP.0000000000000055
208. Wassersug RJ, Oliffe JL (2009) The social context for psychological distress from iatrogenic gynecomastia with suggestions for its management. J Sex Med 6(4):989–1000. https://doi.org/10.1111/j.1743-6109.2008.01053.x

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Carlotta Pozza[1] · Riccardo Selice[2] · Arcangelo Barbonetti[3] · Valeria Hasenmajer[1] · Francesco Lotti[4,5] · Davide Menafra[6] · Daniela Pasquali[7] · Andrea Sansone[8] · Andrea M. Isidori[1,9] · Vincenzo Rochira[10,11]

✉ Carlotta Pozza
carlotta.pozza@uniroma1.it

Vincenzo Rochira
vincenzo.rochira@unimore.it

1 Division of Endocrinology and Andrology, Department of Experimental Medicine, Sapienza University, Rome, Italy

2 Unit of Andrology and Reproductive Medicine, Department of Systems Medicine, University Hospital of Padova, Padova 35100, Italy

3 Andrology Unit, Department of Clinical Medicine, Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy

4 Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Florence, Italy

5 Andrology and Gender Endocrinology Unit, University Hospital Careggi (AOUC), Florence, Italy

6 Department of Clinical Medicine and Surgery, Section of Endocrinology, Diabetology, Andrology and Nutrition, Federico II University of Naples, Naples, Italy, Unit of Andrology and Male and Fenale Reproductive and Sexual Medicine, Federico II University of Naples, Naples, Italy

7 Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Naples, Italy

8 Chair of Endocrinology and Medical Sexology, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

9 Centre for Rare Diseases (Endo-ERN Accredited), Policlinico Umberto I, Rome, Italy

10 Endocrinology Unit, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

11 Endocrinology Unit, Department of Medical Specialties, Azienda Ospedaliero-Universitaria Policlinico di Modena, Ospedale Civile di Baggiovara, Modena, Italy