

PREPUBERTAL AND PUBERTAL GYNECOMASTIA

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Physiology and molecular mechanisms

Gynecomastia is defined as the growth of the male mammary gland to become palpable and/or visible.

During embryogenesis, the differentiation of the mammary gland and surrounding estroma, as well as the areola and the nipple, is similar in the two sexes. It is well established that estrogens stimulate breast growth. The production of estrogens during pregnancy is very high. For this reason, breast development is frequently present at birth in the two sexes. Furthermore, several growth factors (EGF, TGF α , IGF-1), progesterone, and GH have also been implicated in mammary growth. However, little is known about the mechanisms modulating differentiation and development of the mammary gland in fetal life [1].

The gonadal activity of the embryonic and fetal testes with their high secretion of testosterone do not generate a sexual dimorphism in the breast development of the newborn. This is interesting, because it has been speculated that in the absence of androgen action, such as in the complete form of the androgen insensitivity syndrome, mammary over development is observed [2]. Moreover, it is generally accepted that the estrogen/androgen balance is an important factor in adult gynecomastia [3, 4], and some experimental evidence indicates that testosterone inhibits estrogen-induced mammary epithelial cell proliferation and suppresses estrogen receptor expression [5]. Even though many questions remain, the central role of estrogens and its receptors on mammary development is well accepted.

Estrogens are synthesized from androgens by cells containing the cytochrome P450 enzyme aromatase, which is transcribed from the CYP19 gene. Typically, these are granulosa cells of the ovaries and syncytiotrophoblast cells of the placenta. However, many other cells do also express aromatase, such as, mesenchymal cells of adipose tissue, including those of the breasts, central nervous system cells, testicular Leydig cells, etc. [6]. The CYP19 gene is located in chromosome 15q21. It has 10 exons and different promoters in different tissues [6]. The coding sequence, exons 2-9 transcribes the same protein in every tissue. In men, and in post menopausal women the origin of estrogens (estradiol and estrone) is mainly extra gonadal, originating from gonadl and adrenal androgen precursors. Even though extragonadal estrogens contribute to serum estradiol and estrone, the importance of the local synthesis of estrogens is the possibility to act as a paracrine stimulation in selected targets.

In prepubertal boys, after the first trimester of life, circulating estrogen levels are very low, barely detectable with the usual methodology. Furthermore, sex hormones (mainly testosterone and estradiol) circulate in blood strongly

bound to a specific protein, sex hormone binding globulin (SHBG). The affinity constant of testosterone for SHBG is greater than that of estradiol, and therefore, it retains testosterone in serum preferentially (lower free testosterone). Serum SHBG increases during the first trimester of life, to gradually decrease thereafter during prepuberty [7]. At puberty, there is a sharp increase in testicular testosterone secretion and a moderate increase in serum estradiol concentration (usually below 25 pg/ml even in advanced puberty and adulthood [8]). Furthermore, there is a decrease in serum SHBG which might favour testosterone entrance over that of estradiol in target cells. The normal serum estrogen levels of boys in the presence of high testosterone concentrations do not usually stimulate mammary tissue development. However, a transient derangement of the equilibrium of estrogens and androgens might be present during normal puberty (see below).

In target tissues, estrogens enter cells and bind to specific receptors, belonging to a family of transcription factors, to modulate gene expression in the nucleus. Two different types of estrogen receptors, alpha and beta (ER α y ER β), with different tissue distribution, have been described. In the last years, presence of steroid hormone receptors [9], including ERs [10], in the cell membrane has been described. In these instances the mechanism of action rather than genomic, is mediated by activating signal transduction at the membrane and rapid cell responses.

Classification of gynecomastia in children and adolescents

Finally, when the described mechanisms of breast development are disturbed, an excessive growth of mammary tissue might occur in males, i. e. , gynecomastia. For the analysis of this clinical condition in children and adolescents, it is convenient to take into account the age of onset of gynecomastia: 1) in newborns at birth, 2) during prepuberty (from 2 months to 11 years of age), and 3) during adolescence (11- to 20-year-old boys).

1. Neonatal Gynecomastia.

As previously stated, newborn gynecomastia is relatively frequent, approximately 60 % [11]. It is a benign condition. It is usually resolved in a few weeks, even though it might occasionally last several months. Fluid discharge from the nipple can be present. This is probably the result of the effect of hormones secreted by the fetoplacental unit during pregnancy [12]. On physical examination, the two breast glands are palpable behind the areolas. They are usually symmetrical. The possibility that what is palpated is not the mammary gland is always present. It could be an abnormal nodule, particularly if it is not symmetric or with different consistency. During follow up mammary nodules should disappear.

2. Prepubertal Gynecomastia

Prepubertal gynecomastia is not frequent, but when present, it is a sign of concern. Occasionally might be a sign of complete precocious puberty in boys.

A careful clinical examination is important. A family history of gynecomastia or other endocrine disturbances should be recorded. It is important to discard the use of cosmetics with estrogens in the family,

particularly in babies, or the accidental ingestion of hormonal pills. In some areas estrogen containing food products are used, such as estrogen treated farm animals.

Since gynecomastia might be a sign of a systemic disturbance, physical examination must be complete, including the degree of sexual development and testicular volume and consistency. Excessive tenderness of the breasts is a frequent complaint. The degree of mammary development can be evaluated using Tanner's criteria for normal adolescents girls. It is also convenient to register longitudinal and transverse diameters of gland borders to compare gland size in follow up examinations. Gland consistency and other palpation characteristics should be evaluated by an experienced observer, particularly in obese children. It is possible that the palpable mass is not mammary gland. Indeed, some tumors, lipoma or vascular tumors, might grow below the areola. An ultrasound study might be of help in these cases [13].

The most frequent causes of prepubertal gynecomastia are listed in table 1. Exogenous estrogen ingestion is more common in early prepuberty, and it might need a careful interrogation to be diagnosed. However, it might not be detected. A clinical characteristic of gynecomastia produced by synthetic estrogens is a strong pigmentation of the areolas and nipples.

Table 1. Etiology of prepubertal gynecomastia

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| Administration of estrogens or estrogenic compounds (androgens or other substrates for aromatase, clomiphene, phytoestrogens, xenoestrogens) |
| Administration of non estrogenic drugs (digoxine, hrGH) |
| Testicular or adrenal tumors |
| HCG secreting tumors |
| Aromatase excess syndrome (familial hyperestrogenism) |
| Central or peripheral precocious puberty |
| Mammary tumors of different cell composition (usually unilateral) |
| Idiopathic gynecomastia. |

In our experience, gynecomastia secondary to testicular tumors has been always associated with palpable testicular nodules (Sertoli cell tumors or Leydig cell tumors). In the case of Sertoli cell tumors, pronounced gynecomastia predominates over signs of androgen stimulation, while in Leydig cell tumors, signs of androgen development predominate, and gynecomastia might be absent. Sertoli cell tumors might be one manifestation of syndromes of multiple congenital anomalies, such as Peutz-Jeghers syndrome (loss of function mutation of serine-threonine kinase, LKB1) or Carney complex (loss of function mutation of the protein kinase A regulatory subunit) [14, 15]. In hCG secreting germinoma, androgenic precocious puberty predominates, but gynecomastia might also be detected. These tumors have different localizations (intracranial, mediastinal, abdominal and

gonadal). Excessive hCG tumoral production stimulates Leydig cell testosterone secretion producing pituitary-gonadotropin independent precocious puberty [16].

Feminizing adrenal tumors of children are rare. It has been postulated that feminization might result from excessive extraglandular aromatization of androstendione [17], or from an aberrant expression of PII and I.3 promoters of the aromatase gene in the adrenal tumor [18].

Prepubertal gynecomastia has been reported in familiar hyperestrogenism [19] or aromatase excess syndrome [20], sometimes producing estrone, rather than estradiol excess [21]. So far, very few patients with these gene mutations have been reported. However, mild gene alterations might explain some cases of idiopathic prepubertal gynecomastia.

Treatment of prepubertal gynecomastia depends on the etiology. The possibility of regression will depend, apart from removing the cause, on the degree of abnormal growth and the time of evolution of the process. When it is grossly visible or painful, and it does result in obvious psychological disturbance for the boy, it should be removed surgically. It is important for this procedure to be carried out by an experienced surgeon.

3. Pubertal Gynecomastia

Different from prepubertal gynecomastia, breast development in boys occurs frequently at puberty. It is usually transient and moderate, not requiring medical or surgical intervention. Prevalence studies are variable, but most estimations indicate that it is present in around 30 to 60 % of adolescent boys [22].

Table 2. Etiology of pubertal gynecomastia

Physiologic gynecomastia of adolescence

Causes listed in Table 1 (feminizing tumors, drugs, familiar gynecomastia)

Primary hypergonadotropic gonadal dysfunction

Klinefelter syndrome (47,XXY and variants)

XX males

Androgen insensitivity syndrome (with ambiguous external genitalia)

Defects in testosterone biosynthesis (with ambiguous external genitalia)

True hermaphroditism (with ambiguous external genitalia)

Other causes of hypergonadotrophic hypogonadism (infections, chemotherapy external radiation)

Secondary hypogonadotrophic gonadal dysfunction

Hyperthyroidism

Hepatic damage

Idiopathic

The progressive changes taking place during testicular sexual maturation can produce, within certain metabolic and hormonal sensitivity contexts, a visible and palpable unilateral or bilateral mammary growth. When these changes are moderate (usually less than Tanner's stage 3) and of short

duration (less than 3-4 months), they usually regress spontaneously. However, this sign is of considerable concern for the patients and their parents.

The adolescent should be questioned about the use of drugs or anabolic steroids and he should undergo a careful physical examination. This should include an evaluation of the degree of sexual development and testicular volume. Pseudogynecomastia (usually fat accumulation) should be discarded. Before diagnosing pubertal gynecomastia as a "normal" variation of sexual development, other causes of gynecomastia should be ruled out. Apart from the etiologies listed in Table 1, pubertal gynecomastia can be a sign of primary or secondary hypogonadism, and also of intersexual states (Table 2). In 1998, Sher, Migeon and Bercovitz [23] analyzed the etiologies of 60 adolescent boys with gynecomastia greater than 4 cm in diameter, aged 10-20 years of age. Endocrine anomalies were detected in 7 subjects, Klinefelter syndrome, XX male, primary testicular failure, hepatocarcinoma. Different pathological processes were diagnosed in another 8 patients, and 45 subjects were labeled as idiopathic.

Klinefelter syndrome is a relatively frequent sex chromosomal anomaly (47, XXY) affecting 1 in 500 males. It associates hypergonadotrophic hypogonadism, small testes with azoospermia and intellectual deficit. Behavioral and school difficulties are frequent. Since gonadal dysfunction becomes evident at puberty, diagnosis is seldom made before adolescence. Moreover, sometimes, signs are mild and diagnosis is not made, even in adults. Uni or bilateral cryptorchidism is frequent among boys with Klinefelter syndrome (1/80). Puberty onset is usually at the right age, with pubic hair and genital development but testis remain small and of higher consistency. Hypogonadism or micropenis might be present. Gynecomastia is frequent. Even though serum testosterone might reach normally low values, serum estradiol is relatively high, and it is assumed that an abnormal estradiol/ testosterone ratio favors mammary development. Seminiferous tubules deterioration is progressive, ending in hyalinization and a further decrease in serum testosterone. In these conditions, replacement testosterone treatment improves hypogonadism, but not infertility. When gynecomastia disturbs patient's everyday life, surgical removal of the breasts is indicated.

XX male testicular dysgenesis is much less frequent. A SRY gene translocation to a X chromosome or to an autosome might explain this condition [24]. Another possibility is the presence of a mosaicism in which the SRY gene is present in the gonads but not in peripheral leukocytes [25]. Clinical presentation is similar to that of Klinefelter syndrome, including gynecomastia, but without intellectual deficit nor short stature.

Some patients with intersex, 46, XY karyotype and ambiguous external genitalia develop gynecomastia at puberty (androgen insensitivity syndrome, true hermaphroditism, 17 β -hydroxysteroid dehydrogenase deficiency). When virilization is important, they might have been considered normal males with hypospadias, who are now developing pubertal gynecomastia. The mechanisms of gynecomastia are different in each instance. In the androgen insensitivity syndrome [26], lack of androgen action and Leydig cell overstimulation secondary to excessive gonadotrophins determine an increase of estrogen secretion and of estrogen sensitivity of breast tissue. In true hermaphroditism the ovarian tissue is stimulated at puberty [27]. Most patients have a 46,XX karyotype, but 7 & of the patients have a 46,XY karyotype. In

17 β -hydroxysteroid dehydrogenase deficiency type III [28], testes preferentially secrete androstendione over testosterone. Excessive androstendione is converted into estrone by peripheral aromatase. The high estrogen/androgen ratio favors the development of gynecomastia.

Gynecomastia has been described in patients with hypogonadotropic hypogonadism [29]. In our experience, it is moderate and not frequent. Theoretically, it might be secondary to an abnormal estrogen/androgen ratio in the breasts.

Gynecomastia is one of the signs of altered function of the hypothalamo-pituitary-gonadal axis in hyperthyroidism [30]. These patients have elevations of testosterone, SHBG and estradiol [31]. It is possible that the high SHBG level will favor the action of estrogens. Correction of hyperthyroidism improves gynecomastia.

Chronic hepatic insufficiency in adults is associated with gynecomastia. However, in prepuberty this problem has not been reported [32]. No information is available in adolescents with chronic hepatic insufficiency.

Apart from "physiological" pubertal gynecomastia, usually moderate and reversible (Tanner's stages 2 and 3), in other cases pubertal gynecomastia is considered "idiopathic" [23]. As previously stated, when size and duration exceed certain limits, treatment is considered.

Treatment has an esthetic purpose, intending to improve the psychosocial disturbance that this "feminine" body characteristic. Less frequently, tenderness or pain is the main complaint. Treatment depends on the cause. Classic treatment is mastectomy. It is very important that an experienced surgeon in plastic or breast surgery carries out this procedure. We have frequently seen the unfortunate consequences of inappropriate surgery, even necrosis of the areola. In most cases results are good. Medical treatment with anti-estrogens or aromatase inhibitors has been used [33], but effects are often partial or temporary. It is possible that third generation aromatase inhibitors (anastrozole) might be of help in some cases [19].

Conclusions

In summary, in the evaluation of gynecomastia in pediatrics, it is important to consider the age of the patient. In prepubertal boys it is always a matter of concern. In pubertal boys, and depending on size and duration, it is

probably a variation of normal puberty. However, presence of other signs might alert towards the possibility of an organic disorder.

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