



“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”

M. Bonomi^{1,2} · B. Cangiano^{1,2} · S. Cianfarani^{3,4,5} · A. Garolla⁶ · D. Gianfrilli^{7,8} · F. Lanfranco⁹ · G. Rastrelli¹⁰ · E. Sbardella^{7,8} · G. Corona¹¹ · A. M. Isidori^{7,8} · V. Rochira^{12,13}

Received: 11 June 2024 / Accepted: 23 July 2024
© The Author(s) 2024

Abstract

Purpose Andrological pathologies in the adulthood are often the results of conditions that originate during childhood and adolescence and sometimes even during gestation and neonatal period. Unfortunately, the reports in the literature concerning pediatric andrological diseases are scares and mainly concerning single issues. Furthermore, no shared position statement are so far available.

Methods The Italian Society of Andrology and Sexual Medicine (SIAMS) commissioned an expert task force involving the Italian Society of Pediatric Endocrinology and Diabetology (SIEDP) to provide an updated guideline on the diagnosis and management of andrological disorders from childhood and adolescence to transition age. Derived recommendations were based on the grading of recommendations, assessment, development, and evaluation (GRADE) system.

Results A literature search of articles in English for the term “varicoceles”, “gynecomastia”, “fertility preservation”, “macroorchidism”, “precocious puberty” and “pubertal delay” has been performed. Three major aspects for each considered disorder were assessed including diagnosis, clinical management, and treatment. Recommendations and suggestions have been provided for each of the mentioned andrological disorders.

Conclusions These are the first guidelines based on a multidisciplinary approach that involves important societies related to the field of andrological medicine from pediatric to transition and adult ages. This fruitful discussion allowed for a general agreement on several recommendations and suggestions to be reached, which can support all stakeholders in improving andrological and general health of the transitional age.

Keywords Transitional age · Transition guidelines · Transition andrology · Andrological diseases · Adolescence andrology · Childhood andrology

Introduction

Many of the andrological pathologies that andrologists face in their adult patients, concerning genital, hormonal, reproductive, oncological, sexual, and psychological aspects are the results of conditions that originate during childhood and adolescence and sometimes even during gestation and neonatal period. For this reason, andrology is the medical specialty that must deal with men’s health and reproductive

function not only during adulthood but more correctly from birth, or even gestation, to ageing of male subjects. Indeed, it is well known that male gonads, together with the hypothalamic GnRH-secreting neurons and the pituitary gonadotroph cells are extremely sensitive to many different factors (i.e. genetic, environmental, chemical, physical, etc... events) that can influence their correct development and functionality during gestation, neonatal age up to puberty and transitional age [1–3]. Therefore, the role of the andrologist is extremely important not only for adult but also pediatric patients. Indeed, an andrological examination should be recommended routinely to all male subjects both in the

Extended author information available on the last page of the article

prepubertal and post-pubertal period. The andrological evaluation of neonatal, pediatric, and adolescent patients is fundamental in acquiring an early diagnosis of many andrological disorders such as disorders of sexual development, structural disease of the genital organs, normal and abnormal puberty, undescended testes, genital tumors, gonadal function, and its relationship to growth, virilization, fertility and gender identity. These pathologies, if not diagnosed with routine screenings, could affect prepubertal, pubertal and post-pubertal subjects, and a different approach would be needed for each age range. Frequently observed disorders are cryptorchidism, varicocele, hydrocele and funicular cysts, inguinal hernia, phimosis, and hypospadias. Less frequently observed disorders are orchitis-epididymitis (i.e. mumps), testicular torsion, microlithiasis, Leydig cells hyperplasia and gynecomastia. Rare observed disorders are gonadal cancer, hypogonadism, and ambiguous genitalia.

Although in the last 5 years an increasing number of papers looking foetal programming and minipuberty have been published, the reports in the literature concerning other pediatric andrological diseases are not so copious and they are mainly concerning single issues [4–12].

Aim of the present paper was to analyze the state of the art regarding the clinical evidence on several different andrological disorders affecting pubertal, and transitional age and to provide a shared position statement of the Italian Societies for Andrology and Sexual Medicine (SIAMS) in collaboration with the Italian Society for Pediatric Endocrinology and Diabetology (SIEDP). Three major aspects for each considered disorder were assessed: diagnosis, clinical management, and treatment. A Part 2 of these guidelines will follow with coverage of other specific conditions such as DSD, micropenis, hypospadias, cryptorchidism, epididymitis-orchitis, testicular torsion, testis cancer.

Material and methods

A literature search of articles in English for the term “varicoceles”, “gynecomastia”, “fertility preservation”, “macroorchidism”, “precocious puberty” and “delayed puberty” has been performed. In this guideline, we will provide recommendations regarding the evaluation and management of different andrological disorders during childhood and transitional age based on the GRADE (grading of recommendations, assessment, development, and evaluation) system for grading both the quality of evidence and the strength of recommendations [13]. According to this system, the strength of recommendation will be divided into ‘strong’, indicated by the number 1 and ‘we recommend’, and ‘weak’ indicated by the number 2 and ‘we suggest’. The grading of the quality of evidence

is denoted as follows: ⊕○○○ for very low-quality evidence; ⊕⊕○○ for low quality; ⊕⊕⊕○ for moderate quality; and ⊕⊕⊕⊕ for high quality [13].

Varicocele

Epidemiology

Varicocele prevalence in paediatric age widely ranges from 4.0% to 35% with an age-dependent increase. In boys younger than 10 years, prevalence is < 1% [14–16]. Prevalence starts rising at age 11–12 years [14, 17] and peaks in late adolescence varying between 14% [14] and 27% [17, 18]. In studies from the general population, most boys have a varicocele which is palpable with Valsalva maneuver (corresponding to Dubin’s grade 1 as described below) [17]; in urological studies, a varicocele which is already visible at the scrotum physical examination without Valsalva maneuver (corresponding to Dubin’s grade 3 below described) is much more frequent (up to 70%) [19].

Pathophysiology

On the left side, the spermatic vein drains into the renal vein at 90° angle, which is a predisposing factor for varicocele. Age is a predictor probably because of the rapid growth occurring during puberty [16, 20]. Accordingly, taller, and leaner boys are at higher risk [16, 20]. Lower testis volume, greater penis length and girth are further statistically significant predictors [16, 20]. However, a clear pathogenic mechanism was not identified for these. Inheritance has a role only for higher graded varicocele and no relationship was found for familiar history of varicose veins [21]. Longitudinal studies assessing the natural history of untreated varicocele in terms of fertility are limited, biased and conflicting [22–24].

Clinical picture

Varicocele can be subclinical (i.e., detected only by ultrasound) or clinically detectable, palpable as a “bag of worms”. Only rarely, it is painful (3%) [19]. Almost 90% of varicoceles are left-sided, around 10% are bilateral, and only a minority are right-sided [14]. Right-sided varicoceles in children and adolescents may be a rare sign of Wilms’ tumour [25].

Diagnostic evaluation

Suggestions and recommendations R1.1 We recommend assessing varicocele by physical examination in recumbent and standing position. (1, ⊕⊕⊕○).

R1.2 We suggest using color Doppler ultrasound to further characterize and grade the varicocele. (2, ⊕ ⊕ ○○).

R1.3 We recommend using ultrasound to accurately assess testicular hypotrophy or asymmetry. (1, ⊕ ⊕ ○○).

Evidence According to Dubin's classification, grade I varicocele is palpable with Valsalva maneuver, grade II is palpable without Valsalva, grade III is visible without Valsalva [26].

Testicular ultrasound might be helpful in confirming and better characterizing the varicocele [27]. It allows the exact evaluation of the varicose veins' extension and dilation according to Sarteschi/Liguori scoring system [28, 29].

Testicular volume or semen analysis, as surrogate markers of future fertility, have been assessed by cross-sectional or short-term retrospective studies. Data on the effect of varicocele on testis volume are conflicting with studies reporting no [30] or small [31] effect and other reporting a progressive decrease for Dubin's grade 2 and 3 varicoceles [32]. Testis volume asymmetry > 20% has been associated with significant impairment in semen parameters (66% with impaired sperm motility) [33].

Remarks Varicocele assessed either by physical examination or color Doppler ultrasound must be performed in recumbent and standing position with Valsalva maneuver. Ultrasound may be used for confirmation, as only palpable varicoceles deserve treatment. The Sarteschi/Liguori classification divides varicoceles in five grades, depending on presence of varicosities. Grade IV and V of Sarteschi/Liguori classification correspond to Dubin's grade III. Scrotal ultrasound may be useful for testis volume assessment—using Lambert's formula (length*width*height*0.71)—since, in adolescents, clinical evaluation could be inaccurate in detecting hypotrophy [34–36]. Evidence on semen analysis in adolescents with varicocele is still limited.

Therapeutic management

Suggestions and recommendations

R1.4 We suggest offering treatment in adolescents with testicular hypotrophy or asymmetry (difference > 20%). (2, ⊕ ⊕ ○○).

R1.5 We suggest considering pain and discomfort for decision making about varicocele treatment, despite evidence is limited. (Expert opinion).

R1.6 We suggest lymphatic sparing surgery or percutaneous embolization, although, at present, no technique has demonstrated to be better. (2, ⊕ ⊕ ⊕ ○).

R1.7 We suggest only monitoring for patients not candidate for surgical treatment. (Expert opinion).

Evidence A recent meta-analysis of the available randomized clinical trials (RCTs) [37] shows that surgery corrects varicocele in more than 85% of cases. As compared with clinical observation, intervention is associated with slightly increased testis volume and higher total sperm count [37]. However, only four and two RCTs were available for these outcomes, respectively [37]. There is not enough evidence for drawing conclusions on future paternity [37]. Pain was rarely assessed; however, treatment resolved it in > 90% of cases [37].

There is not enough evidence for indicating which is/are the best surgical technique/s to use in adolescents [37]. Since the most common adverse event is hydrocele and this is limited by lymphatic sparing surgery, this should be preferred [37]. Percutaneous embolization techniques may be an alternative to surgery and radiological risk should be considered especially for younger patients [38, 39].

Remarks Although conflicting and limited, present evidence suggests that treatment of varicocele should be offered in adolescents with hypotrophy or asymmetry > 20% of testis volume [32, 33, 40–42]. However, this could lead to overtreatment since asymmetry is a frequent finding also in adolescents without any scrotal disease [43]. In case of conservative approach, the clinical follow up should include periodical physical examination, ultrasound, and semen analysis. The latter should be considered with caution and limited to patients with Tanner stage V. Asymmetry worsening over time may be more informative. Follow-up studies suggest that a catch-up grow in testicular volume of treated adolescents and young adults can occur [44]. However, the evidence on the natural history of untreated varicoceles in adolescence is lacking. Since regular monitoring of subclinical varicoceles is suggested in adulthood [45], a similar approach might be a good clinical practice also in adolescence [44].

Gynecomastia

Epidemiology

Gynecomastia is the benign enlargement of the male breast caused by proliferation of glandular tissue [46]. It can be unilateral or bilateral, most commonly the latter [47, 48]. It is the most common breast alteration in males, being mostly physiologic during infancy, puberty, and old

age [49, 50]. Prevalence rates are 65–90% in newborns, 22–69% in adolescents, and 24–65% in men between 50 and 69 years [51, 52].

Pathophysiology

The causes of gynecomastia are multifactorial, and 25% of all cases appear idiopathic. Among the underlying causes, three groups of triggers are distinguished: physiologic, pathologic and pharmacologic/toxic [50, 52].

The peak prevalence in adolescents is observed during mid-puberty, when the sex hormones surge [53]. Underlying endocrinopathy cannot be detected in most cases, and spontaneous regression can be expected within 6 months or less but may persist up to 1–2 years [54].

Clinical picture

Gynecomastia of infancy can persist for several weeks after birth and can cause mild breast discharge called “witch’s milk” [46]. Gynecomastia of infancy is not associated with any sequels or aberrations of development; typically, it does not persist after the first year of life. Detection of glandular breast tissue requires a careful physical examination feeling a firm, rubbery, finely lobular mobile disc of tissue that extends concentrically from under the nipple and areola. Although it is mostly bilateral, it is often asymmetrical and can occur unilaterally. Psychological or sexual issues at puberty are among the chief complaints, although pain may be frequent [51].

Diagnostic evaluation

Suggestions and recommendations R2.1 We suggest that the initial screening to rule out lipomastia, obvious breast cancer, or testicular cancer might be performed by a pediatrician, a general practitioner, or another non-specialist. (2, ⊕ ⊕ ○○).

R2.2 We recommend that in those cases where a thorough diagnostic workup is warranted, it should be performed by a specialist in endocrinology/pediatric endocrinology/andrology. (1, ⊕ ⊕ ⊕ ○).

R2.3 We recommend testis and breast US to rule out possible tumors. (1, ⊕ ⊕ ⊕ ○).

Evidence The primary goal of the initial evaluation should be to confirm the presence of palpable glandular tissue and rule out the suspicion of malignant breast tumor or testicular tumor. In the setting of simple lipomastia, the condition can be diagnosed and followed up by palpation; the finding of palpable glandular tissue suggest the need for breast and testicular US [51]. Persistence during adolescence or a new and rapidly developing condition may warrant further

workup [52]. To rule out malignant tumors, breast (ultrasound and mammography) [55] and testis (ultrasound) imaging is mandatory [56].

Andrological history should include information on cryptorchidism, the onset of puberty, and symptoms of testosterone deficiency. Information on general illness, use of medications, use of anabolic–androgenic steroids (AAS), alcohol, cannabis, and drug abuse should also be noted [57]. Thyroid disorders should also be ruled out.

If gynecomastia is mild and non-progressive or if adolescent gynecomastia, according to Tanner stage, is a very likely diagnosis, the initial laboratory evaluation comprises serum early-morning (i.e., before 10 AM) total testosterone, estradiol, LH, and FSH levels. In less straightforward cases, the basic laboratory workup should include also TSH, FT3, FT4, SHBG, prolactin, β-hCG, and liver and renal function tests [46, 49–51, 57].

Remarks To which degree pubertal gynecomastia needs diagnostic workup is controversial; in the expert hands, it can be restricted to physical examination [47]. The initial screening of gynecomastia might be performed by a pediatrician or a general practitioner to rule out the presence of mammary or testicular cancer. The workup of gynecomastia should be carried out by a specialist in endocrinology/pediatric endocrinology/andrology.

Therapeutic management

Suggestions and recommendations R2.3 We do not recommend medical therapy for pubertal gynecomastia, which resolves spontaneously within 24 months in more than 90% of cases. (1, ⊕ ⊕ ○○).

R2.4 We recommend withdrawal of interfering drugs, whenever feasible, treatment of concomitant disorders, and discontinuation of substances of abuse or inducing drugs, before considering a specific treatment for gynecomastia. (1, ⊕ ⊕ ⊕ ○).

R2.5 We suggest surgical treatment only for patients with long-lasting gynecomastia, which does not regress spontaneously, or which causes considerable psychosocial and psychological distress, after puberty completion. (2, ⊕ ⊕ ○○).

Evidence In cases of gynecomastia of puberty (or adulthood) with negative physical and hormonal investigations, there is a fair chance that the condition will disappear spontaneously, especially if it is of recent onset [47, 54].

If gynecomastia is severe, does not resolve, and does not have a treatable underlying cause, some medical therapies may be attempted. Data on pharmacologic therapy for pubertal gynecomastia is partial and scarce, with insufficient high-quality evidence-based original research on efficacy

and safety in transitional age. Pharmacological treatment can have an advantage in relieving behavioral and psychological distress [58]. There are three classes of medical treatments: androgens, anti-estrogens and aromatase inhibitors. Tamoxifen has been used in gynecomastia of puberty with partial response in most cases (90%) but a complete response in < 10% [58, 59]. Gynecomastia in Klinefelter syndrome boys, which incidence (35.6%) is not increased compared with typically developing boys, can be reduced or resolved by testosterone supplementation, potentially preventing the need for surgery [52].

When medical therapy is ineffective, particularly in cases of longstanding gynecomastia, when the breast enlargement is severe, painful, socially embarrassing, or when there is suspicion of breast malignancy, then surgical therapy is appropriate [50, 60].

Remarks Surgical treatment should not be offered until after an observation period has been allowed [47]. Surgical treatment should be postponed preferably until after completion of puberty to minimize the chance of recurrent gynecomastia after surgery. In cases of pubertal gynecomastia where the disease causes considerable psychosocial and psychological distress, surgical treatment is justified [60, 61].

Particular attention should be paid to gynecomastia in boys of prepubertal age, a rare finding, which is not anticipated by normal hormone fluctuations and warrants thorough evaluation to rule out an underlying pathology [46].

Fertility preservation

From childhood and adolescence to transition age, some categories of male patients should receive counseling related to fertility preservation (FP). These categories are: (i) patients who are candidates for potentially sterilizing therapies; (ii) patients with Klinefelter syndrome (KS) and other aneuploidies; (iii) subjects with disorders of sex development (DSDs); (iv) transgender persons assigned male at birth (T-AMAB) undergoing gender affirming treatments.

Epidemiology

- i) Many types of cancers, both solid and hematologic, and more rarely immunological and rheumatological conditions of adolescents, can affect males during the transitional age. The incidence of childhood cancer has steadily increased since the 1950s [62] and the incidence in children aged 0–14 is reported of 140.6 per million person/year [63].
- ii) KS (47,XXY syndrome) and other chromosomal abnormalities leading to male infertility, such as

the presence of more than two supra-numerous X chromosomes, or different types of mosaicisms, occurs in about 152–223 cases per 100,000 males and is the most frequent (numerical) chromosomal disorder in males and, although nowadays the greater use of prenatal diagnosis techniques is allowing ever-increasing percentage of early diagnoses, it is currently often diagnosed in adulthood [64–66]. KS is one of the most frequent causes of infertility, affecting 10–15% of azoospermic infertile men [67].

- iii) DSD is a group of congenital conditions characterized by atypical development of chromosomal, gonadal or anatomic sex that leads to a discordance between the genital appearance and the chromosomal sex and infertility [68, 69]. DSD worldwide incidence is approximately 1:1000–4500 live births. Excluding simple cryptorchidism and hypospadias the incidence rate among subjects with a 46,XY karyotype to have a DSD has been estimated to be 1 in 20,000 births [70].
- iv) The prevalence of referral gender incongruence is increasing worldwide [71]. A recent demographic report shows that over 1.6 million people identify themselves as transgender in the United States (0.6% of population), and they account for 1.4% of young people between 13 and 17 years old [72, 73]. Fertility preservation represents an increasingly crucial aspect of healthcare nowadays for T-AMAB individuals who want to become women and at the same time who wish to have their own biological offspring in the future.

Pathophysiology

- i) Young males who undergo cancer treatments (chemo/radiotherapy or surgical treatments affecting the genital tract) are more frequently affected by infertility than females of the same age [74]. It has been estimated that one third of cancer survivors treated at prepubertal age will be azoospermic at adult age while one fifth will be oligozoospermic [75–77]. So far, there are no data available on the future fertility of subjects treated for immunological and rheumatological pathologies in adolescence.
- ii) Boys with KS progressively lose their spermatogenic capacity. From early puberty to mid-puberty, there is a histological change starting with relatively normal seminiferous tubules, reduced germ cells, and normal Sertoli/Leydig cells to the adult condition showing extensive fibrosis and hyalinization of the seminiferous tubules [78]. Up to 8% of men with KS have spermatozoa in the ejaculate [79, 80] and in about 60% the sperm recovery can be obtained through testicular sperm extraction [81, 82]. US imaging can help in identifying progressive time

and puberty-related deterioration of testicular structure [83].

- iii) Infertility in DSD can be due to anatomical defects, abnormal gonad development, prophylactic gonadectomy and hormone replacement therapy to induce and sustain puberty [84].
- iv) Gender affirming hormonal therapies (GAHT), which are an integral part of gender transition in T-AMAB, have a significant impact on fertility [85]. Moreover, gender affirming surgery (GAS) usually leads to permanent sterility in these patients [71].

Clinical picture

The clinical presentation can be different according to the patient's age and issue. Unlike post-pubertal youth, childhood subjects have not yet reached spermatogenesis and therefore have immature testicles presenting only spermatogonial stem cells. Cancer patients and T-AMAB usually have testicles that function normally while subjects affected by KS and DSD have always dysgenetic testicles with altered architecture of the seminiferous tubules.

Diagnostic evaluation

Suggestions and recommendations R3.1 We recommend testicular physical examination and pubertal stage evaluation in all pediatric patients to guide towards the appropriate FP option. (1, ⊕ ⊕ ⊕ ⊕).

R3.2 We suggest providing adequate counseling on FP to these patients and their parents. (Expert Opinion).

Evidence More studies suggest that in case of risk of gonadal damage and fertility loss, patients should be referred to the infertility specialist at diagnosis and before gonadotoxic treatments [86, 87]. The updated guidelines emphasize the importance of addressing gonadotoxicity and FP in all patients with reproductive potential, including the pediatric population [62]. Parents need to be made aware of and be receptive to fertility preservation options while young patients must also be receptive to discussions about fertility preservation, suitable to their age [88–90].

Remarks It is essential that the clinical team has a detailed history and knowledge of the hormonal pattern, testicular physiology, and pubertal stage [87] to choose the appropriate protocol of FP. Early conversations should be initiated at the time of diagnosis to provide patients/parents with accurate information regarding FP options and to maximize the number of strategies available to the patient [62, 91].

Therapeutic management

Suggestions and recommendations R3.3 We recommend sperm cryopreservation in all young boys able to collect semen and in which it is possible to retrieve mature sperm. (1, ⊕ ⊕ ⊕ ⊕).

R3.4 We suggest discussing testicular biopsy with tissue banking in case of prepubertal or azoospermic subjects. (2, ⊕ ⊕ ○○).

Evidence Cryopreservation of semen is a well-established method for fertility preservation in post-pubertal males and in patients before gonadotoxic treatments [92, 93]. For boys who have not yet reached spermatogenesis, investigational options provide significant hope for the future. These techniques rely upon the testicular biopsy and cryopreservation of either whole tissue or spermatogonial stem cells (SSCs). While testicular biopsy is considered safe and effective for adults, its use for prepubertal patients is currently considered experimental and its suitability should be discussed very carefully with the treatment team on a case-by-case basis [94–98].

Remarks Sperm cryopreservation is a very valuable approach that should be performed in all boys who are able to collect sperm and who are at risk of infertility or undergoing potentially sterilizing therapies [94, 99].

For pre-pubertal subjects who cannot produce an ejaculate, or patients who do not have sperm in their semen, a piece of testicular tissue can be surgically removed to be frozen and stored [62, 87]. Although conflicting and limited, present evidence suggests that future advances in the use of cryopreserved testicular tissue will represent the only fertility chance for these males facing sterilizing conditions [96–98, 100, 101]. However, this option should be considered experimental and there is no guarantee that the stored sperm or testicular tissue will enable subject to father in the future [62].

Macroorchidism

Epidemiology

Macroorchidism is a condition that describes an increase of testicular volume, extremely rare in children and adolescents and usually included in the clinical presentation of some genetic syndromes or endocrine disorders.

Pathophysiology

Several genetic syndromes have been associated with macroorchidism, but the most frequently described in literature are the X-fragile syndrome (caused by a CGG

trinucleotide repeat expansion in the *FMRI* gene) [102] and the loss-of-function mutations in immunoglobulin superfamily member 1 (*IGSF1*) gene. This latter gene deficiency causes specific impairment of pituitary secretion which can be responsible of testicular enlargement, such as central hypothyroidism (with prolonged proliferation of Sertoli cells) and high FSH values [103, 104]. Other X-linked syndromes in which macroorchidism is described are the Clark-Baraitser syndrome [105] and the Atkin-Flaitz syndrome [106]. Among autosomic genetic disorders, McCune-Albright [107–109] and Beckwith-Wiedemann syndrome [110] have been associated with macroorchidism.

Apart from genetic conditions, also some rare endocrine disorders can present with macroorchidism such as FSH-secreting pituitary adenomas [111, 112], congenital adrenal hyperplasia (CAH) [113] and severe aromatase deficiency [114]. Finally, in this context, it is important to early identify testis enlargement due to testicular tumors or lymphomas with testicular localization [115].

Clinical picture

Macroorchidism can be unilateral or bilateral. Testicles are usually enlarged (above +2SD curve for age) [116] with normal consistency (unless the cause is testicular cancer). Bilateral macroorchidism increase the suspicious of genetic and endocrine syndromes but also, in some cases, lymphomas [115]. Sometimes McCune-Albright syndrome can also present with unilateral enlargement [108]. In fragile X syndrome, patients have significantly larger testes throughout childhood, with true macroorchidism becoming manifested usually just prior to puberty [116–118] while it is always post-pubertal (or even with adult onset) in IGSF1 deficiency [119].

A sudden enlargement of the testicles may depend on testicular tumors, lymphomas or FSH-secreting pituitary adenomas [111, 112, 115, 120].

The association with other signs typical of genetic syndromes can help in differential diagnosis. Fragile X syndrome is usually characterized by intellectual disability and a characteristic phenotype [117, 121]. For this reason, the diagnosis is often made around 2–3 years of age, long before the appearance of macroorchidism. IGSF1 deficiency is characterized by central hypothyroidism, delayed pubertal testosterone rise, variable prolactin deficiency, variable GH deficiency, metabolic syndrome [104, 122, 123]. Café-au-lait skin pigmentation and precocious puberty can suggest McCune-Albright syndrome [109].

Diagnostic evaluation

Suggestions and recommendations **R4.1** We recommend assessing macroorchidism with a complete physical exami-

nation, and to use Prader orchidometer to evaluate testicular volume compared with the reference percentiles for age. (1, ⊕ ⊕ ⊕ ⊕).

R4.2 We recommend testicular ultrasound to rule out testicular lesions and to better assess testicular volume. (1, ⊕ ⊕ ⊕ ⊕).

R4.3 We suggest evaluating laterality, age at onset and onset time and eventual associate conditions such as mental retardation, café-au-lait skin pigmentation, precocious puberty, phenotypic abnormalities, signs of hypothyroidism or CAH to guide differential diagnosis. (2, ⊕ ⊕ ⊕ ⊕).

R4.4 We suggest measuring LH, FSH, early morning Testosterone, TSH and FT4 in children and adolescents with macroorchidism. (2, ⊕ ⊕ ⊕ ⊕).

Evidence Literature on macroorchidism is limited to case reports and case series in the different clinical context. The assessment of the condition is always performed with physical examination. Testicular ultrasound is the gold standard technique to exclude testis nodules [56]. Outside the context of testicular masses there is not enough evidence on the role of testicular ultrasound features in describing macroorchid testicles [109, 110]. Testicular function is usually normal [124]. In IGSF1 deficiency, FSH is increased with normal Inhibin B, LH and testosterone can be reduced at the beginning of pubertal development, while thyroid function assessment always shows central hypothyroidism (low/normal TSH and low FT4) [119, 125].

Remarks Macroorchidism should be assessed by physical examination using Prader orchidometer and compared with a table of percentiles for age. Ultrasound is recommended to exclude testicular nodules and for a better assessment of testicular volume. A complete medical history and physical examination is mandatory to address the suspicious of genetic syndromes. FSH, TSH and FT4 assessment is encouraged if no genetic mutation is already known.

Therapeutic management

Due to heterogeneity of the macroorchidism pathophysiology, patients' management should refer to specific underlying diseases, bearing in mind that no effect on testicular volume is expected, since macroorchidism is more a clinical presentation than a pathological condition. In case of finding of testicular lesions, as for adults, specific treatment is recommended [126].

Precocious puberty

Definition and epidemiology

Precocious puberty is defined as the development of secondary sexual characteristics before 8 years of age in

girls and 9 years in boys [127]. The estimated incidence in American girls is 1 in 5000–10000 [128]. An observational study from Spain reported an incidence of central precocious puberty between 0.02 and 1.07 cases per 100 000 persons/year [129]. The prevalence is sexually dimorphic, being higher in girls than in boys (15–20 girls for every boy) who more often show an organic cause [130].

Pathophysiology

Precocious puberty is classified into two major categories based on the aetiology: Central Precocious puberty (CPP), or GnRH dependent precocious puberty, is secondary to the early activation of the hypothalamus–pituitary–gonadal (HPG) axis [131, 132]. The most relevant causes are reported in Table 1. Peripheral Precocious Puberty (PPP), or GnRH independent precocious puberty, is due to the increase of sex steroids from endogenous or exogenous sources, independently of HPG axis activity [133]. It is less common than CPP and the most common causes in boys are reported in Table 1.

Clinical picture

In boys, testicular volume equal or greater than 4 mL is the first sign of puberty in CPP whereas a testicular volume less than 4 mL in presence of signs of puberty suggests PPP. Pubic and axillary hair, body odor, hyperpigmentation of penis and scrotum, accelerated growth and advanced bone age are the clinical signs of precocious puberty. Skin examination is necessary for detection of facial acne or oily skin and cutaneous pigmentation (café-au-lait spots). Unilateral testicular enlargement, or the detection of testicular nodules on palpation, suggests a testicular tumor.

Diagnostic evaluation

Suggestions and recommendations R5.1 We recommend in a boy younger than 9 years measuring testicular volume with Prader's orchidometer and to compare the signs of puberty with the Tanner's staging method. (1, ⊕ ⊕ ⊕ ⊕).

R5.2 We recommend performing left hand and wrist X-rays for bone age assessment in all boys with precocious puberty. (1, ⊕ ⊕ ⊕ ○).

Table 1 Causes of Precocious puberty

Central Precocious puberty (CPP)

A) CNS congenital alterations:

- Hypothalamic hamartoma
- Suprasellar arachnoid cysts
- Glioma or neurofibromatosis type 1
- Tuberous sclerosis
- Hydrocephalus
- Septo-optic dysplasia
- Chiari II malformations and myelomeningocele

B) CNS acquired alterations:

- Tumours: astrocytoma, ependymoma, pinealoma, hypothalamic and optic glioma, craniopharyngioma, dysgerminoma (non-HCG secreting), meningioma
- Injury: trauma, cranial irradiation, cerebral palsy, infections
- Genetics: loss of function mutation of the MKRN3 gene, gain of function mutation of kisspeptin (KISS1) and its receptor (KISSR) genes, chromosomal abnormalities (Latronico 2016)
- Environmental: adopted children, early exposure to sex steroids

Causes of peripheral precocious puberty (PPP)

- Congenital adrenal hyperplasia (CAH)
- McCune-Albright syndrome
- Testosterone producing tumours
 - Adrenal carcinoma or adenoma
 - Leydig cell tumour
- Gonadotropin /HCG producing tumours
 - Dysgerminoma
 - Choriocarcinoma
 - Hepatoblastoma
 - Chorionepitelioma
 - Teratoma
 - Gonadoblastoma
- Familial male-limited precocious puberty (testotoxicosis due to germline activating mutation of the LH receptor gene)
- Exposure to exogenous sex steroids
- Hypothyroidism (Van Wyk-Grumbach syndrome)

R5.3 We recommend testing all patients with high suspicion for precocious puberty with GnRH stimulation test, basal LH value being less reliable to exclude precocious puberty. (1, ⊕ ⊕ ⊕ ○).

R5.4 We recommend performing brain MRI in all boys with CPP. (1, ⊕ ⊕ ⊕ ⊕).

R5.5 We recommend measuring early-morning testosterone, dehydroepiandrosterone sulphate (DHEA-S), 17-OH-progesterone and hCG in boys with suspicion for PPP. (1, ⊕ ⊕ ⊕ ○).

R5.6 We recommend ultrasound of testes in boys with PPP and testosterone excess and brain MRI in all boys with PPP associated with detectable hCG. (1, ⊕ ⊕ ⊕ ○).

R5.7 We suggest genetic investigations in boys with CPP and a clear family history of CPP. (2, ⊕ ⊕ ○○).

Evidence Advanced bone age is a hallmark of precocious puberty [134]. The bone age of patients with precocious puberty is generally advanced by 2 years or more compared to chronological age. However, the absence of advanced bone age is not a reason to discontinue follow-up assessment when increased growth velocity and other clinical signs of progressive puberty are present [135].

Careful history, physical exam and growth velocity assessment should guide the evaluation [127]. The child with bilateral enlarged testicles, for example, is most likely to have central precocious puberty, FSH causing the expansion of seminiferous tubule volume. Conversely, the child with clear signs of puberty associated with prepubertal sized testicles is more likely to have PPP, and the child with unilateral testicular enlargement may have a testicular tumour. Testing should be directed accordingly. The gold-standard for biochemical diagnosis of CPP is the assessment of gonadotropins, mainly LH, after stimulation with exogenous GnRH or GnRH agonists. A LH peak response to GnRH equal or greater than 5 mU/mL is consistent with CPP, whereas FSH levels are of limited utility [136]. With the development of laboratory methods based on monoclonal antibodies which have higher sensitivity and specificity than radioimmunoassay methods, baseline random LH assessment has been proposed to evaluate the activation of the gonadotropic axis thus avoiding the need to perform a GnRH stimulation test. However, several studies have shown that the diagnostic value of basal LH is variable, with sensitivity ranging from 60 to 100% [137].

Once the diagnosis of CPP is made, brain MRI scan is mandatory to exclude the presence of congenital or acquired underlying pathology. Most organic causes of CPP are congenital or acquired CNS alterations and even some cases of PPP may be secondary to hCG secreting brain tumour (i.e., dysgerminoma).

Gain-of-function mutations in the genes encoding Kisspeptin and Kisspeptin receptor (*KISS1* *KISS1R*) and

loss-of-function mutations encoding Makorin ring finger 3 (*MKRN3*) and Delta Like Non-Canonical Notch Ligand 1 (*DLK1*) have been shown in patients with CPP [132]. *MKRN3* mutations are now the most common genetic defect associated with CPP, with an overall frequency of ~ 10% (up to 46% in cases of familial CPP) [132].

In PPP both LH and FSH are suppressed, and androgens are elevated. DHEAS is used to screen for adrenal tumours or adrenal pathology whereas 17-hydroxyprogesterone is used to screen for congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency [138]. High levels of testosterone suggest a testicular tumour. Testicular tumours may be too small to palpate, and ultrasound scan is useful in unexplained PPP cases and may reveal impalpable Leydig cell tumours.

Once the diagnosis of PPP is made, the diagnostic workup will require appropriate imaging and, often, biopsy of the suspected lesion.

Remarks The development of laboratory methods that make use of monoclonal antibodies such as immuno-fluorometric, immunochemiluminometric, and electro-chemiluminometric assays has led some authors to suggest that baseline random LH could be used to assess the activation of the gonadotropic axis, avoiding the need for testing of the GnRH-stimulated LH concentration. However, determining the diagnostic cut-off for the basal LH level is difficult because of a lack of normative data and variability among assays, ranging from 0.1 to 1.5 IU/L.

Therapeutic management

Central precocious puberty

Suggestions and recommendations R5.8 We recommend GnRH agonist therapy as the standard of care in children with CPP. GnRHa therapy should be started soon if the child is at or beyond Tanner stage III, particularly when skeletal maturation is advanced of 2 or more years. (1, ⊕ ⊕ ⊕ ○).

R5.9 We recommend, during treatment, monitoring of pubertal progression, growth velocity every 3 to 6 months, and skeletal maturation every 6 to 12 months. (1, ⊕ ⊕ ○○).

R5.10 We suggest discontinuing GnRH agonist treatment between 13.0 and 13.5 years of bone age. (2, ⊕ ○○○).

Evidence Long-acting GnRH agonists have been the gold-standard treatment since the mid-1980s [136]. The two main aims of such therapy are to preserve adult height and to prevent psychosocial difficulties. The most important clinical criterion for starting a child on GnRHa treatment is the documented progression of pubertal development, which is based on the recognition that many patients with CPP have

a slowly progressive or non-progressive form and achieve adult height within their target range without therapy [139, 140].

GnRH agonists continuously stimulate the pituitary gonadotropin secreting cells thus desensitizing them and reducing LH release and, to a lesser extent, FSH. Several GnRH agonists are available in various depot forms, and their approval for use and recommended doses in precocious puberty vary in different countries. All available GnRH agonists are effective despite their different routes of administration, dosing, and duration of action. GnRH agonists induce the regression of pubertal symptoms, reduce growth velocity, and decrease bone-age advancement.

No randomised controlled trials have assessed long-term outcomes after GnRH agonist treatment. Few controlled prospective studies have been performed in children, and many conclusions rely on expert opinions. For example, height outcomes have been assessed mainly by comparisons between achieved adult height and predicted height before treatment [139–141]. Therefore, the evidence supporting the use of GnRH agonists in all children with CPP is weak. The efficacy of such therapy in increasing adult height is undisputed only in early-onset CPP. The real impact of therapy on psychosocial wellbeing needs to be ascertained with rigorously designed longitudinal studies.

GnRH agonists are generally well tolerated and effective. Monitoring of such therapy should consist of assessment of pubertal stage and growth velocity every 3 to 6 months with periodic (every 1–2 years) evaluation of skeletal maturation. Progression of pubertal signs, high growth velocity and advancement of bone age indicate poor compliance, treatment failure, or incorrect diagnosis, demanding further assessment. Regular monitoring of LH and testosterone levels during GnRH agonist therapy has been proposed and suppression of LH to less than 4.5 IU/L during GnRH stimulation test is considered an acceptable target in patients on GnRH agonist therapy. However, an adequate clinical and anthropometric evaluation is a reliable mirror of the endocrine status and may avoid blood tests which should be reserved to patients with poor response to therapy.

The optimal time to discontinue GnRH agonist treatment is difficult to fix because of variability in chronologic age, bone age and degree and duration of secondary sexual characteristics prior to initiation of therapy. In addition, data from boys with CPP are extremely limited. Pubertal signs reappear within months after cessation of GnRH agonist treatment. It could be reasonable to decide when to stop therapy according to patient and family preference with the intent of synchronizing pubertal development with the patient's peers.

Remarks GnRH agonists are usually well tolerated. Treatment can be associated with headaches, rash, gastrointestinal

complaints. These adverse effects are generally transient and resolve spontaneously or with symptomatic treatment. Local complications such as sterile abscesses can result in a loss of efficacy, and anaphylaxis has been described in rare cases.

Long-term fertility has not been fully assessed, but preliminary data showed normal reproduction function. Bone mineral density can decrease during GnRH agonist therapy, but subsequent bone mass accrual is preserved, and peak bone mass is not affected. A potential negative effect on BMI was postulated but the available data suggest that long-term GnRH agonist treatment does not cause or aggravate obesity.

Peripheral precocious puberty

Suggestions and recommendations R5.11 We recommend treating (surgically or medically) the underlying cause of PPP. (1, ⊕ ⊕ ⊕ ⊕).

R5.12 We recommend combination therapy with antiandrogen and third-generation aromatase inhibitor in severe cases of PPP with androgen excess. (1, ⊕ ○○○).

Evidence GnRH-independent forms of precocious puberty are a spectrum of many different conditions often associated with androgen hypersecretion secondary to tumours. Together with the removal of the neoplasm responsible for androgen excess, combination therapy with a potent antiandrogen, bicalutamide, and a third-generation aromatase inhibitor is effective in reducing virilization, growth rate, skeletal maturation and improving adult height. However, no large-scale longitudinal study has been conducted so far and most available data come from case reports. It should be also remarked that these treatments are mostly off-label in several countries. Treatment of PPP should be personalized according to the aetiology. Children with congenital adrenal hyperplasia, for example, will benefit from glucocorticoid therapy. In poorly controlled patients with long-lasting hyperandrogenism associated with bone age advancement secondary CPP may occur thus requiring treatment with GnRH agonists [142, 143].

Remarks PPP is much less common than CPP and poses ongoing challenges in the pursuit of the optimal clinical management. Collaborative multicentre long-term clinical trials are needed to achieve sufficient evidence to guide to the appropriate therapy and to unveil the ultimate outcomes for these children.

Delayed puberty

Epidemiology

Delayed puberty (DP) in male subjects is defined as the failure to enter puberty by the age of 14 years or to

complete the process, with a prolonged tempo of pubertal development (above 5.2 years) [144, 145]. It is a common condition affecting up to 2% of adolescents [146, 147]. DP is particularly prevalent in boys and for this reason is across-the-board of andrology and both pediatric and adult endocrinology. In boys is mainly related (63–64% of cases) to a self-limited condition called Constitutional Delay of Growth and Puberty (CDGP) [148–151] whereas the remaining part consists of pathological conditions determining a functional (FHH, 18–20% of DP) or persistent hypogonadism ($\approx 15\%$) [146–149, 152–154].

Pathophysiology

CDGP is the most frequent form of DP and represent a paraphysiological condition which is self-limited with a common familial component [151, 155]. DP due to hypogonadism conditions can be classified according to the origin of the failure of the hormonal axis in primary or hypergonadotropic hypogonadism (gonadal origin) and central, or hypogonadotropic hypogonadism (pituitary/hypothalamic origin). Primary hypogonadism can be caused by acquired gonadal damage (including radio- and chemo-therapy), congenital causes such as chromosomal abnormalities (Klinefelter syndrome, KS) or other genetic conditions impairing gonadal development, gonadotropin receptors or steroidogenic enzymes [156].

Central hypogonadism can be distinguished in functional (usually reversible) and organic forms. FHH is usually determined by a dysregulation of the hypothalamic-pituitary–gonadal axis caused by metabolic and/or inflammatory condition (which include malnutrition, chronic illnesses, inflammatory diseases such as coeliac disease and inflammatory bowel diseases, and anorexia nervosa). Organic forms include acquired structural (i.e. invasive, infiltrative, inflammatory, ischemic or even iatrogenic lesions to the pituitary and/or the hypothalamus) and congenital alterations such as multiple pituitary hormone defects (MPHD) and congenital isolated hypogonadotropic hypogonadism (CHH), which represent the main differential diagnosis of CDGP [144, 150, 151, 154, 155, 157].

Clinical picture

The clinical presentation of DP in boys is the failure to start and/or complete physiologic testicular development (Fig. 1), the lack of growth spurt and, usually, the lack of signs of virilization such as pubic hair and secondary sexual characteristics. Bone age is always delayed of at least 1 year in CDGP and is extremely helpful in guiding the diagnostic work-up. Boys with CGDP are usually referred to the specialist for short stature secondary to the delayed pubertal growth spurt but their slow “tempo” of growth does not

impair the achievement of a normal adult height corresponding to their genetic growth potential (midparental height). Olfactory defects, hearing impairment, midline defects and kidney/teeth abnormalities as well as other syndromic features can be present if the delay of puberty is part of a more complex disease [151, 158].

Diagnostic evaluation

Suggestions and recommendations R6.1 We recommend an expert evaluation of pubertal development in any boy presenting with DP defined by no testicular enlargement equal or above 4 mL (measured with Prader’s orchidometer) at the age of 14 years, or the failure to progress adequately in his pubertal development.

(1, ⊕ ⊕ ⊕ ⊕).

R6.2 We recommend measuring LH, FSH, early-morning total testosterone (T) levels and assessing bone age with left hand and wrist radiography in all subjects with DP. (1, ⊕ ⊕ ⊕ ⊕).

R6.3 We recommend performing karyotype and testicular ultrasound (US) in patients with high gonadotropin levels to rule in/out Klinefelter syndrome and/or testicular damage. (1, ⊕ ⊕ ⊕ ⊕).

R6.4 We suggest adopting a “wait and see” strategy evaluating the patient after six months in all subjects with DP and Tanner stage 1, LH levels above 0.2 IU/L but below the upper limit range, T above 0.7 nmol/L and bone age below 13 years. (2, ⊕ ⊕ ⊕ ⊕).

R6.5 We suggest testing with GnRH stimulation test all patients with DP, LH levels below 0.2 IU/L and T below 0.7 nmol/L or no clinical (no Tanner stage 2 achievement) and hormonal (LH and T increase) progressions after six months of “wait and see” strategy. (2, ⊕ ⊕ ⊕ ⊕).

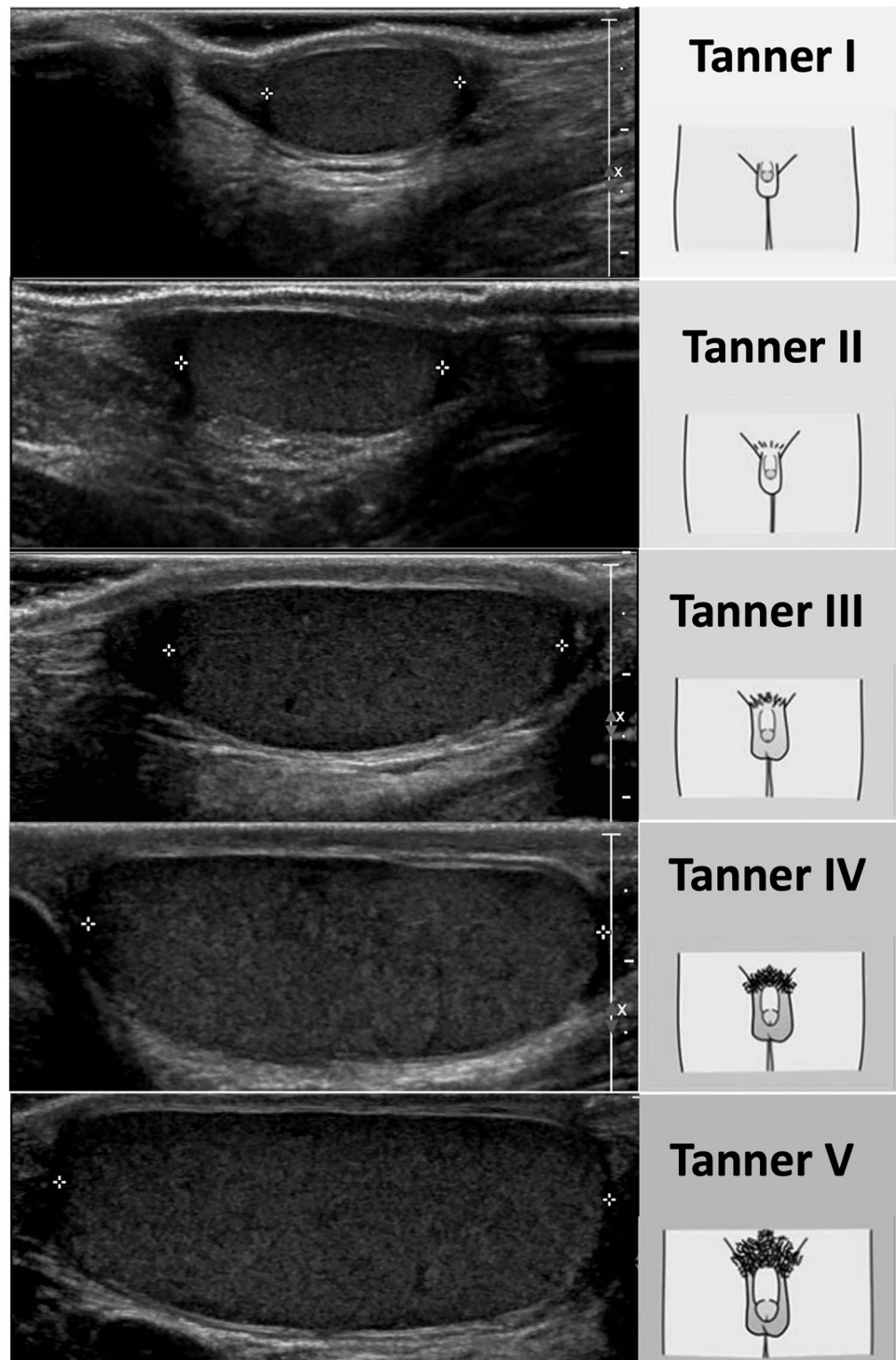
R6.6 We recommend excluding other diseases causing acquired secondary hypogonadism in all subjects with DP, low T and low gonadotropins and not responsive to GnRH test or bone age above 13 years. (1, ⊕ ⊕ ⊕ ⊕).

R6.7 We recommend referring patients with a diagnosis of CHH to a dedicated center to perform a genetic analysis and family counselling. (1, ⊕ ⊕ ⊕ ⊕).

Evidence The primary goal of the clinician is to define a true DP, which could be a failure to start or to complete the process in due time, and its underlying cause. The definition of a standard pubertal timing in male is defined by a testicular volume equal or above 4 mL before the age of 14 years [158, 159] and the normal duration of the entire process should not exceed 5.2 years [144, 145]. Nonetheless, also the absence of growth spurt by the age of 16 is a sign of DP [160].

Accurate clinical history collection is mandatory including a detailed family history for pubertal or

Fig. 1 Normal testicular ultrasound according to Tanner stages



endocrinological disorders. Yet, both CHH and CDGP patients show positive familiar history which can also be shared between them with up to 10% of family members of CHH patients showing a delayed puberty [161].

At the physical examination, it is important to evaluate the Tanner stage of the patient [158, 159], his growth and the so called “red flags” reported in Table 2, as hallmarks

of likely CHH [3, 150, 151, 162, 163]. Furthermore, the interruption of pubertal development after its onset is suggestive for hypogonadism with a bone age above 13 years [158, 164].

High gonadotropin levels, especially along with low T, are clearly diagnostic of primary (hypergonadotropic) hypogonadism [146]. Among the main causes of

Table 2 The “red flags” suggesting a diagnosis of CHH

Red flags
Cryptorchidism
Microorchidism (< 1.1 mL)
Micropenis (according SD for age) doi:10.1001/archpedi.1943.02010160019003
Hypospadias
Hypo-/anosmia
Hearing defects
Midline defects (i.e., cleft lip and/or palate)
digital abnormalities
Bimanual synkinesis or “mirror movements”
Dental dysgenesis/agenesis

hypergonadotropic hypogonadism there are: anorchia, testicular damages including traumatic, iatrogenic (i.e. chemo- and/or radiotherapy), infective ones and congenital causes such as KS (although patients with KS usually have a spontaneous onset of puberty that may not reach full virilization at its end). A karyotype (for KS) and testicular ultrasound scan (for gonadal damage), along with personal history, are necessary for the diagnosis [158, 165]. If negative, the patient should be referred to a tertiary centre to evaluate other genetic conditions and complex syndromes.

At the beginning of pubertal development LH and FSH are very low and the use of ultrasensitive assays (i.e., detection limit < 0.1 IU/L) are required to discriminate between prepubertal from pubertal children based on their concentration [166]. At this respect, reference ranges for both gonadotropins using ultrasensitive assays are available for all ages including the pubertal transition period [167]. LH levels above 0.2 IU/L are suggestive for the beginning of puberty [168]. Similarly, early-morning T levels, measured with specific and ultrasensitive assays, above 0.7 nmol/L are a biochemical sign of the beginning of puberty which will be followed by pubertal signs within 12–15 months [169]. If T and gonadotropins are below these thresholds, the finding is consistent with CDGP or hypogonadotropic hypogonadism. GnRH test measures the previous stimulation of the pituitary gonadotropes from GnRH. A boy with DP responding to GnRH test (i.e. LH peak > 5 IU/L) [170], will likely start puberty within 1 year [168, 171].

Remarks Although the expert evaluation of pubertal development should be started when no signs of pubertal development are present by the age of 14 years in boys, we should anticipate this assessment at the age of 9 years in all children with documented risk of persistent hypogonadism.

It should be emphasized that bone age should be assessed by an experienced physician (pediatric endocrinologist, endocrinologist, radiologist) or by a validated digital system.

Table 3 causes of functional hypogonadotropic hypogonadism (FHH)

Causes of FHH
Malnutrition and Anemia
Anorexia nervosa
Low energy availability/relative energy deficit
Coeliac disease
IBD
Systemic inflammatory disease
Obesity
Other chronic illnesses
Other endocrine diseases (i.e. hyperPRL, cushing, etc.)
Drugs

It is worth mentioning that GnRH testing is useful to unmask the beginning of puberty, but not to perform a differential diagnosis between CDGP and CHH [150, 171]. Indeed, in patients with initial elevation of LH and T or testing positive to GnRH stimulation test, it might be considered adopting a “wait and see” strategy for other six months, starting further specific investigation if there is no pubertal progression during this period.

In patients presenting a bone age discordant with the hormone levels or with no signs of pubertal onset, it is important to exclude all the possible causes of acquired hypogonadotropic hypogonadism including both functional (Table 3) and organic/structural forms. A short child with DP should be screened for excluding celiac disease (anti-transglutaminase antibodies), hypothyroidism (FT4 and TSH), GH deficiency (IGF1) and inflammatory bowel disease (fecal calprotectin). In case of subnormal or low normal range IGF1 levels, boys with DP and growth impairment should be tested for GHD using specific dynamic evaluations according to the indication of the consensus of the GH society [172, 173] after priming with sex steroids [174–178].

It is also important to evaluate pituitary function (including cortisol, ACTH, FT4, FT3, IGF1 levels, prolactin) and perform brain MRI scan with pituitary and olfactory tract assessment in all subjects with a suspected diagnosis of hypogonadotropic hypogonadism.

Genetic analysis (e.g., Targeted-Next Generation Sequencing or Whole Exome Sequencing techniques) could be helpful to diagnose CHH if a known causative gene variant is found [3, 179, 180]. Genetic analyses and counselling should be performed in tertiary referral center due to the expertise needed for genetic counselling and rare variants interpretation [179, 180].

Treatment

Suggestions and recommendations R6.8 We recommend starting the proper treatment once the diagnosis of hypogonadism is well-established. (1, ⊕ ⊕ ⊕ ⊕).

R6.9 We recommend starting treatment with intramuscular or transdermal testosterone once the diagnosis of hypergonadotropic hypogonadism is confirmed. (1, ⊕ ⊕ ⊕ ⊕).

R6.10 We suggest discussing the possible initial treatment with gonadotropins in patients with hypogonadotropic hypogonadism. (2, ⊕ ⊕ ⊕ ⊕).

R6.11 We suggest using low-dose sex steroids for three to six months, which can be repeated for other three to six months, to distinguish DP due to CDGP from CHH and to manage patients' psychological discomfort. (2, ⊕ ⊕ ⊕ ⊕).

R6.12 We recommend treating the underlying causes of FHH and to consider a medical treatment for puberty induction whenever this is not feasible. (1, ⊕ ⊕ ⊕ ⊕).

Evidence It is important to treat persistent forms of hypogonadism once diagnosed. It is worth noting that the acceleration of bone maturation and the risk of reducing near adult height are increased when treatment is started too early. Treatment from the age of 12 years has been shown to be safe in patients with a high risk of hypogonadism [181–185].

Testosterone is the only effective treatment for patients with hypergonadotropic hypogonadism. The evidence regarding the induction of puberty using testosterone esters with lower half-life (monthly or weekly testosterone esters) are stronger than the ones regarding either testosterone gel or long half-life intramuscular testosterone undecanoate. However, transdermal formulations seem to be a more viable and practical solution compared to long acting undecanoate. Current formulations of oral testosterone are not recommended due to the low half-life and the high hepatic concentrations [186].

Gonadotropins have shown potential efficacy for both reproductive and non-reproductive outcomes in patients with hypogonadotropic hypogonadism [187]. Treatment with both gonadotropins and testosterone should be discussed with these patients and their family, providing a balanced counselling about benefits and drawbacks [184, 186].

The approach to the boy with high suspicion of CGDP can be “wait and see” or based on therapy with low-doses of testosterone [150, 151, 158]. A trial with low-doses of androgens has proved to increase the growth rate of these patients, as well as improve their quality of life and psychological well-being [188–190]. Moreover, recent evidence suggests a potential impact on near adult height in CDGP boys and on body proportion of CHH patients treated with low-dose sex steroids [148, 174, 187, 190]. This low-dose testosterone therapy (50 mg per month for 3–4 months)

Table 4 therapeutic schemes for low doses of sex steroids

Formulation	Dosing and administration
Testosterone enanthate	50 mg i.m. monthly
Testosterone gel 2%	10 mg every second day

could be proposed to patients with decreased self-esteem, psychosocial difficulties in the interaction with peers [148, 158, 188–191]. This approach has been shown to be safe not affecting bone age maturation and adult height [188–190], and it could be useful for preventing a lower bone mass in adulthood [192].

Remarks The treatment with low-dose sex steroids can be performed with both intramuscular esters and transdermal formulations, as reported in Table 4.

It should also be noted that patients who do not achieve spontaneous puberty after one year of treatment with low-dose sex steroids are to be considered hypogonadotropic hypogonadism and should undergo careful evaluation of pituitary function [165].

Finally, in patients with a diagnosis of DP undergoing a trial with low-dose sex steroids, if growth spurt does not occur during the treatment, FHH should be reconsidered.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40618-024-02435-x>.

Declarations

Conflict of interest Authors declare no competing interest.

Compliance with ethics standards This article does not contain any studies with human or animal subjects.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, 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 changes were made. 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/4.0/>.

References

- Juul A, Almstrup K, Andersson A, Jensen TK, Jorgensen N, Main KM, Rajpert-De Meyts E, Toppari J, Skakkebaek NE (2014) Possible fetal determinants of male infertility. *Nat Rev Endocrinol* 10:553–562. <https://doi.org/10.1038/nrendo.2014.97>
- Skakkebaek NE, Rajpert-De Meyts E, Main KM (2001) Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod* 16:972–978. <https://doi.org/10.1093/humrep/16.5.972>
- Cangiano B, Swee DS, Quinton R, Bonomi M (2021) Genetics of congenital hypogonadotropic hypogonadism: peculiarities and phenotype of an oligogenic disease. *Hum Genet* 140:77–111. <https://doi.org/10.1007/s00439-020-02147-1>
- Hadziselimovic F, Herzog B (1994) Andrological problems in adolescence. *Ther Umsch* 51:305–313
- Cavarzere P, Sulpasso M, Maines E, Vincenzi M, Gaudino R, Monti E, Chironi C, Tato L, Antoniazzi F (2011) Serum inhibin B levels before and after varicocelectomy in early adolescence. *J Endocrinol Invest* 34:265. <https://doi.org/10.3275/7796>
- Foresta C, Garolla A, Frigo AC, Carraro U, Isidori AM, Lenzi A, Ferlin A (2013) Anthropometric, penile and testis measures in post-pubertal Italian males. *J Endocrinol Invest* 36:287–292. <https://doi.org/10.3275/8514>
- Delfino M, Elia J, Imbrogno N, Argese N, Mazzilli R, Toscano V, Mazzilli F (2012) Testicular adrenal rest tumors in patients with congenital adrenal hyperplasia: prevalence and sonographic, hormonal, and seminal characteristics. *J Ultrasound Med* 31:383–388. <https://doi.org/10.7863/jum.2012.31.3.383>
- Serefoglu EC, Saitz TR, La Nasa JAJ, Hellstrom WJ (2013) Adolescent varicocele management controversies. *Andrology* 1:109–115. <https://doi.org/10.1111/j.2047-2927.2012.00004.x>
- Maggi M, Buvat J (2013) Standard operating procedures: pubertas tarda/delayed puberty—male. *J Sex Med* 10:285–293. <https://doi.org/10.1111/j.1743-6109.2012.02678.x>
- Fast AM, Deibert CM, Van Batavia JP, Nees SN, Glassberg KI (2014) Adolescent varicocelectomy: does artery sparing influence recurrence rate and/or catch-up growth? *Andrology* 2:159–164. <https://doi.org/10.1111/j.2047-2927.2013.00142.x>
- Foresta C, Garolla A, Zuccarello D, Pizzol D, Moretti A, Barzon L, Palu G (2010) Human papillomavirus found in sperm head of young adult males affects the progressive motility. *Fertil Steril* 93:802–806. <https://doi.org/10.1016/j.fertnstert.2008.10.050>
- Pereira NM (1999) Phimosis, hydrocele and varicocele. 3 frequent pathologies in the male child and adolescent. *Acta Med Port* 12:137–143
- 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* 93:666–673. <https://doi.org/10.1210/jc.2007-1907>
- Akbay E, Cayan S, Doruk E, Duce MN, Bozlu M (2000) The prevalence of varicocele and varicocele-related testicular atrophy in Turkish children and adolescents. *BJU Int* 86:490–493. <https://doi.org/10.1046/j.1464-410x.2000.00735.x>
- Stavropoulos NE, Mihailidis I, Hastazeris K, Moissidou R, Louka G, Filiadis I, Zouma E, Danella M, Kalomiris P (2002) Varicocele in schoolboys. *Arch Androl* 48:187–192. <https://doi.org/10.1080/01485010252869270>
- Kumanov P, Robeva RN, Tomova A (2008) Adolescent varicocele: who is at risk? *Pediatrics* 121:53. <https://doi.org/10.1542/peds.2007-0340>
- Zampieri N, Patane S, Camoglio FS (2021) Twenty-year experience with macro-area school screening for andrological disease in paediatric age. *Andrologia* 53:e14209. <https://doi.org/10.1111/andr.14209>
- Gianfrilli D, Ferlin A, Isidori AM, Garolla A, Maggi M, Pivonello R, Santi D, Sansone A, Balercia G, Granata ARM, Sinisi A, Lanfranco F, Pasqualetti P, Foresta C, Lenzi A, 'Amico-Andrologo' Study Group (2019) Risk behaviours and alcohol in adolescence are negatively associated with testicular volume: results from the Amico-Andrologo survey. *Andrology* 7:769–777. <https://doi.org/10.1111/andr.12659>
- Kozakowski KA, Gjertson CK, Decastro GJ, Poon S, Gasalberti A, Glassberg KI (2009) Peak retrograde flow: a novel predictor of persistent, progressive and new onset asymmetry in adolescent varicocele. *J Urol* 181:2717–22. <https://doi.org/10.1016/j.juro.2009.02.038>
- Prabakaran S, Kumanov P, Tomova A, Hubaveshki S, Agarwal A (2006) Adolescent varicocele: association with somatometric parameters. *Urol Int* 77:114–117. <https://doi.org/10.1159/00093902>
- Griffiths L, Vasudevan V, Myers A, Morganstern BA, Palmer LS (2018) The role of inheritance in the development of adolescent varicoceles. *Transl Androl Urol* 7:920–925. <https://doi.org/10.21037/tau.2018.09.02>
- Chu DI, Zderic SA, Shukla AR, Srinivasan AK, Tasian GE, Weiss DA, Long CJ, Canning DA, Kolon TF (2017) The natural history of semen parameters in untreated asymptomatic adolescent varicocele patients: a retrospective cohort study. *J Pediatr Urol* 13:77.e1-77.e5. <https://doi.org/10.1016/j.jpuro.2016.09.008>
- Cayan S, Sahin S, Akbay E (2017) Paternity rates and time to conception in adolescents with varicocele undergoing microsurgical varicocele repair vs observation only: a single institution experience with 408 patients. *J Urol* 198:195–201. <https://doi.org/10.1016/j.juro.2017.01.066>
- Bogaert G, Orye C, De Win G (2013) Pubertal screening and treatment for varicocele do not improve chance of paternity as adult. *J Urol* 189:2298–2303. <https://doi.org/10.1016/j.juro.2012.12.030>
- Erginel B, Vural S, Akin M, Karadag CA, Sever N, Yildiz A, Tanik C, Demir AA, Yanar O, Dokucu AI (2014) Wilms' tumor: a 24-year retrospective study from a single center. *Pediatr Hematol Oncol* 31:409–414. <https://doi.org/10.3109/08880018.2014.930767>
- Dubin L, Amelar RD (1970) Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. *Fertil Steril* 21:606–609. [https://doi.org/10.1016/s0015-0282\(16\)37684-1](https://doi.org/10.1016/s0015-0282(16)37684-1)
- Spaziani M, Lecis C, Tarantino C, Sbardella E, Pozza C, Gianfrilli D (2021) The role of scrotal ultrasonography from infancy to puberty. *Andrology* 9:1306–1321. <https://doi.org/10.1111/andr.13056>
- Bertolotto M, Cantisani V, Drudi FM, Lotti F (2021) Varicocele Classification and pitfalls. *Andrology* 9:1322–1330. <https://doi.org/10.1111/andr.13053>
- Lotti F, Frizza F, Balercia G, Barbonetti A, Behre HM, Calogero AE, Cremers J, Francavilla F, Isidori AM, Kliesch S, La Vignera S, Lenzi A, Marcou M, Pilatz A, Poolamets O, Punab M, Godoy MFP, Quintian C, Rajmil O, Salvio G, Shaer O, Weidner W, Maseroli E, Cipriani S, Baldi E, Degl'Innocenti S, Danza G, Caldini AL, Terreni A, Boni L, Krausz C, Maggi M (2022) The European Academy of Andrology (EAA) ultrasound study on healthy, fertile men: an overview on male genital tract ultrasound reference ranges. *Andrology* 10(Suppl 2):118–132. <https://doi.org/10.1111/andr.13260>
- Khasnavis S, Kogan BA (2015) Natural history of testicular size in boys with varicoceles. *J Pediatr Urol* 11:148.e1-148.e5. <https://doi.org/10.1016/j.jpuro.2015.02.014>

31. Lourdaux P, Vaganee D, Leysen C, De Wachter S, De Win G (2023) Evolution of testicular asymmetry during puberty in adolescents without and with a left varicocele. *BJU Int* 131:348–356. <https://doi.org/10.1111/bju.15914>
32. Kass EJ, Stork BR, Steinert BW (2001) Varicocele in adolescence induces left and right testicular volume loss. *BJU Int* 87:499–501. <https://doi.org/10.1046/j.1464-410x.2001.00144.x>
33. Diamond DA, Zurakowski D, Bauer SB, Borer JG, Peters CA, Cilento BGJ, Paltiel HJ, Rosoklija I, Retik AB (2007) Relationship of varicocele grade and testicular hypotrophy to semen parameters in adolescents. *J Urol* 178:1584–1588. <https://doi.org/10.1016/j.juro.2007.03.169>
34. Oehme NHB, Roelants M, Bruslerud IS, Eide GE, Bjerknæs R, Rosendahl K, Juliusson PB (2018) Ultrasound-based measurements of testicular volume in 6- to 16-year-old boys—intra- and interobserver agreement and comparison with Prader orchidometry. *Pediatr Radiol* 48:1771–1778. <https://doi.org/10.1007/s00247-018-4195-8>
35. Kurtz MP, Migliozi M, Rosoklija I, Zurakowski D, Diamond DA (2015) Accuracy of orchidometry in boys with varicocele. *J Pediatr Urol* 11:185.e1–185.e5. <https://doi.org/10.1016/j.jpuro.2015.02.011>
36. Diamond DA, Paltiel HJ, DiCanzio J, Zurakowski D, Bauer SB, Atala A, Ephraim PL, Grant R, Retik AB (2000) Comparative assessment of pediatric testicular volume: orchidometer versus ultrasound. *J Urol* 164:1111–1114. <https://doi.org/10.1097/00005392-200009020-00048>
37. Silay MS, Hoen L, Quadackaers J, Undre S, Bogaert G, Dogan HS, Kocvara R, Nijman RJM, Radmayr C, Tekgul S, Stein R (2019) Treatment of varicocele in children and adolescents: a systematic review and meta-analysis from the European Association of Urology/European Society for Paediatric Urology guidelines panel. *Eur Urol* 75:448–461. <https://doi.org/10.1016/j.eururo.2018.09.042>
38. Wong S, Vigneswaran G, Maclean D, Bryant T, Hacking N, Maher B, Somani B, Manoharan S, Brownlee E, Griffin S, Modi S (2022) 10-year experience of Paediatric varicocele embolization in a tertiary centre with long-term follow-up. *J Pediatr Urol* 18:113.e1–113.e6. <https://doi.org/10.1016/j.jpuro.2021.12.013>
39. Ierardi AM, Biondetti P, Tsetis D, Del Giudice C, Uberoi R (2023) CIRSE standards of practice on varicocele embolisation. *Cardiovasc Intervent Radiol* 46:19–34. <https://doi.org/10.1007/s00270-022-03293-x>
40. Sigman M, Jarow JP (1997) Ipsilateral testicular hypotrophy is associated with decreased sperm counts in infertile men with varicoceles. *J Urol* 158:605–607
41. Kurtz MP, Zurakowski D, Rosoklija I, Bauer SB, Borer JG, Johnson KL, Migliozi M, Diamond DA (2015) Semen parameters in adolescents with varicocele: association with testis volume differential and total testis volume. *J Urol* 193:1843–1847. <https://doi.org/10.1016/j.juro.2014.10.111>
42. Zavattaro M, Ceruti C, Motta G, Allasia S, Marinelli L, Di Bisceglie C, Tagliabue MP, Sibona M, Rolle L, Lanfranco F (2018) Treating varicocele in 18: current knowledge and treatment options. *J Endocrinol Invest* 41:1365–1375. <https://doi.org/10.1007/s40618-018-0952-7>
43. Vaganee D, Daems F, Aerts W, Dewaide R, van den Keybus T, De Baets K, De Wachter S, De Win G (2018) Testicular asymmetry in healthy adolescent boys. *BJU Int* 122:654–666. <https://doi.org/10.1111/bju.14174>
44. Sansone A, Fegatelli DA, Pozza C, Fattorini G, Lauretta R, Minnetti M, Romanelli F, Lucatelli P, Corona M, Bezzi M, Lombardo F, Lenzi A, Gianfrilli D (2019) Effects of percutaneous varicocele repair on testicular volume: results from a 12-month follow-up. *Asian J Androl* 21:408–412. https://doi.org/10.4103/aja.aja_102_18
45. Ferlin A, Calogero AE, Krausz C, Lombardo F, Paoli D, Rago R, Scarica C, Simoni M, Foresta C, Rochira V, Sbardella E, Francavilla S, Corona G (2022) Management of male factor infertility: position statement from the Italian Society of Andrology and Sexual Medicine (SIAMS): endorsing organization: Italian Society of Embryology, Reproduction, and Research (SIERR). *J Endocrinol Invest* 45:1085–1113. <https://doi.org/10.1007/s40618-022-01741-6>
46. Swerdloff RS, Ng JCM (2000) Gynecomastia: etiology, diagnosis, and treatment. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrere B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trencle DL, Wilson DP (eds) *Endotext*. MDText.com, Inc, South Dartmouth (MA)
47. 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* 176:555–566. <https://doi.org/10.1530/EJE-16-0643>
48. Butler G (2021) Incidence of gynaecomastia in Klinefelter syndrome adolescents and outcome of testosterone treatment. *Eur J Pediatr* 180:3201–3207. <https://doi.org/10.1007/s00431-021-04083-2>
49. Sansone A, Romanelli F, Sansone M, Lenzi A, Di Luigi L (2017) Gynecomastia and hormones. *Endocrine* 55:37–44. <https://doi.org/10.1007/s12020-016-0975-9>
50. Zavattaro M, Motta G, Allasia S, Lanfranco F (2017) Gynecomastia. In: Simoni M, Huhtaniemi I (eds) *Endocrinology of the testis and male reproduction, endocrinology I*. Springer, Cham
51. 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* 7:778–793. <https://doi.org/10.1111/andr.12636>
52. Butler G, Srirangalingam U, Faithfull J, Sangster P, Senniappan S, Mitchell R (2023) Klinefelter syndrome: going beyond the diagnosis. *Arch Dis Child* 108:166–171. <https://doi.org/10.1136/archdischild-2020-320831>
53. Mieritz MG, Raket LL, Hagen CP, Nielsen JE, Talman MM, 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* 100:3752–3759. <https://doi.org/10.1210/jc.2015-2836>
54. Nydic M, Bustos J, Dale JHJ, Rawson RW (1961) Gynecomastia in adolescent boys. *JAMA* 178:449–454. <https://doi.org/10.1001/jama.1961.03040440001001>
55. 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* 20:2797–2805. <https://doi.org/10.1007/s00330-010-1867-7>
56. 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* 15:5332. <https://doi.org/10.3390/cancers15225332>
57. Braunstein GD (2007) Clinical practice. Gynecomastia. *N Engl J Med* 357:1229–1237. <https://doi.org/10.1056/NEJMcp070677>
58. Berger O, Landau Z, Talisman R (2022) Gynecomastia: a systematic review of pharmacological treatments. *Front Pediatr* 10:978311. <https://doi.org/10.3389/fped.2022.978311>
59. Derman O, Kanbur NO, Kutluk T (2003) Tamoxifen treatment for pubertal gynecomastia. *Int J Adolesc Med Health* 15:359–363. <https://doi.org/10.1515/ijamh.2003.15.4.359>

60. Karamchandani MM, De La Cruz KuG, Sokol BL, Chatterjee A, Homsy C (2022) Management of gynecomastia and male benign diseases. *Surg Clin North Am* 102:989–1005. <https://doi.org/10.1016/j.suc.2022.06.003>
61. 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* 43:206–212. <https://doi.org/10.1016/j.adolescence.2015.06.007>
62. Burns KC, Hoefgen H, Strine A, Dasgupta R (2018) Fertility preservation options in pediatric and adolescent patients with cancer. *Cancer* 124:1867–1876. <https://doi.org/10.1002/ncr.31255>
63. Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, Hesselting P, Shin HY, Stiller CA, IICC-3 contributors (2017) International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol* 18:719–731. [https://doi.org/10.1016/S1470-2045\(17\)30186-9](https://doi.org/10.1016/S1470-2045(17)30186-9)
64. Herlihy AS, Gillam L (2011) Thinking outside the square: considering gender in Klinefelter syndrome and 47, XXY. *Int J Androl* 34:348. <https://doi.org/10.1111/j.1365-2605.2010.01132.x>
65. Gies I, Unuane D, Velkeniers B, De Schepper J (2014) Management of Klinefelter syndrome during transition. *Eur J Endocrinol* 171:67. <https://doi.org/10.1530/EJE-14-0213>
66. Bonomi M, Rochira V, Pasquali D, Balercia G, Jannini EA, Ferlin A, ItaliaN Group (2017) Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. *J Endocrinol Invest* 40:123–134. <https://doi.org/10.1007/s40618-016-0541-6>
67. Okada H, Fujioka H, Tatsumi N, Kanzaki M, Okuda Y, Fujisawa M, Hazama M, Matsumoto O, Gohji K, Arakawa S, Kamidono S (1999) Klinefelter's syndrome in the male infertility clinic. *Hum Reprod* 14:946–952. <https://doi.org/10.1093/humrep/14.4.946>
68. Lee PA, Nordenstrom A, Houk CP, Ahmed SF, Auchus R, Baratz A, Baratz Dalke K, Liao L, Lin-Su K, Looijenga LH, Mazur T, Meyer-Bahlburg HFL, Mouriquand P, Quigley CA, Sandberg DE, Vilain E, Witchel S, Global DSD Update Consortium (2016) Global disorders of sex development update since 2006: perceptions, approach and care. *Horm Res Paediatr* 85:158–180. <https://doi.org/10.1159/000442975>
69. Giudice MG, Del Vento F, Wyns C (2019) Male fertility preservation in DSD, XXY, pre-gonadotoxic treatments—Update, methods, ethical issues, current outcomes, future directions. *Best Pract Res Clin Endocrinol Metab* 33:101261. <https://doi.org/10.1016/j.beem.2019.01.002>
70. Sax L (2002) How common is intersex? a response to Anne Fausto-Sterling. *J Sex Res* 39:174–178. <https://doi.org/10.1080/00224490209552139>
71. Oles N, Darrach H, Landford W, Garza M, Twose C, Park CS, Tran P, Schechter LS, Lau B, Coon D (2022) gender affirming surgery: a comprehensive, systematic review of all peer-reviewed literature and methods of assessing patient-centered outcomes (part 1: breast/chest, face, and voice). *Ann Surg* 275:e52–e66. <https://doi.org/10.1097/SLA.0000000000004728>
72. Herman JL, Wilson BD, Becker T (2017) Demographic and health characteristics of transgender adults in California: findings from the 2015–2016 California health interview survey. *Policy Brief UCLA Cent Health Policy Res* 8:1–10
73. D'Amato A, Cascardi E, Etrusco A, Lagana AS, Schonauer LM, Cazzato G, Vimercati A, Malvasi A, Damiani GR, Di Naro E, Trojano G, Cicinelli E, Vitagliano A, Dellino M (2023) “Lights and shades” of fertility preservation in transgender men patients: a clinical and pathological review. *Life* 13:1312. <https://doi.org/10.3390/life13061312>
74. Hamre KES, Ayodo G, Hodges JS, John CC (2020) A mass insecticide-treated bed net distribution campaign reduced malaria risk on an individual but not population level in a highland epidemic-prone area of Kenya. *Am J Trop Med Hyg* 103:2183–2188. <https://doi.org/10.4269/ajtmh.19-0306>
75. Knopman JM, Papadopoulos EB, Grifo JA, Fino ME, Noyes N (2010) Surviving childhood and reproductive-age malignancy: effects on fertility and future parenthood. *Lancet Oncol* 11:490–498. [https://doi.org/10.1016/S1470-2045\(09\)70317-1](https://doi.org/10.1016/S1470-2045(09)70317-1)
76. Ghezzi M, Berretta M, Bottacin A, Palego P, Sartini B, Cosci I, Finos L, Selice R, Foresta C, Garolla A (2016) Impact of bep or carboplatin chemotherapy on testicular function and sperm nucleus of subjects with testicular germ cell tumor. *Front Pharmacol* 7:122. <https://doi.org/10.3389/fphar.2016.00122>
77. Ghezzi M, De Toni L, Palego P, Menegazzo M, Faggian E, Berretta M, Fiorica F, De Rocco PM, Foresta C, Garolla A (2017) Increased risk of testis failure in testicular germ cell tumor survivors undergoing radiotherapy. *Oncotarget* 9:3060–3068. <https://doi.org/10.18632/oncotarget.23081>
78. Gies I, De Schepper J, Goossens E, Van Saen D, Pennings G, Tournaye H (2012) Spermatogonial stem cell preservation in boys with Klinefelter syndrome: to bank or not to bank, that's the question. *Fertil Steril* 98:284–289. <https://doi.org/10.1016/j.fertnstert.2012.04.023>
79. Wu FC, Bancroft J, Davidson DW, Nicol K (1982) The behavioural effects of testosterone undecanoate in adult men with Klinefelter's syndrome: a controlled study. *Clin Endocrinol* 16:489–497. <https://doi.org/10.1111/j.1365-2265.1982.tb02763.x>
80. Kitamura M, Matsumiya K, Koga M, Nishimura K, Miura H, Tsuji T, Matsumoto M, Okamoto Y, Okuyama A (2000) Ejaculated spermatozoa in patients with non-mosaic Klinefelter's syndrome. *Int J Urol* 7:88–94
81. Fullerton G, Hamilton M, Maheshwari A (2010) Should non-mosaic Klinefelter syndrome men be labelled as infertile in 2009? *Hum Reprod* 25:588–597. <https://doi.org/10.1093/humrep/dep431>
82. Corona G, Pizzocaro A, Lanfranco F, Garolla A, Pelliccione F, Vignozzi L, Ferlin A, Foresta C, Jannini EA, Maggi M, Lenzi A, Pasquali D, Francavilla S, Klinefelter ItaliaN Group (2017) Sperm recovery and ICSI outcomes in Klinefelter syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 23:265–275. <https://doi.org/10.1093/humupd/dmx008>
83. 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* 108:2486–2499. <https://doi.org/10.1210/clinem/dgad205>
84. Van Batavia JP, Kolon TF (2016) Fertility in disorders of sex development: a review. *J Pediatr Urol* 12:418–425. <https://doi.org/10.1016/j.jpuro.2016.09.015>
85. Dabel J, Schneider F, Wistuba J, Kliesch S, Schlatt S, Neuhaus N (2023) New perspectives on fertility in transwomen with regard to spermatogonial stem cells. *Reprod Fertil* 4:e220022. <https://doi.org/10.1530/RAF-0022>
86. Redig AJ, Brannigan R, Stryker SJ, Woodruff TK, Jeruss JS (2011) Incorporating fertility preservation into the care of young oncology patients. *Cancer* 117:4–10. <https://doi.org/10.1002/ncr.25398>
87. Picton HM, Wyns C, Anderson RA, Goossens E, Jahnukainen K, Kliesch S, Mitchell RT, Pennings G, Rives N, Tournaye H, van Pelt AMM, Eichenlaub-Ritter U, Schlatt S, ESHRE Task Force On Fertility Preservation In Severe Diseases (2015) A European perspective on testicular tissue cryopreservation for fertility preservation in prepubertal and adolescent boys. *Hum Reprod* 30:2463–2475. <https://doi.org/10.1093/humrep/dev190>

88. Adams E, Hill E, Watson E (2013) Fertility preservation in cancer survivors: a national survey of oncologists' current knowledge, practice and attitudes. *Br J Cancer* 108:1602–1615. <https://doi.org/10.1038/bjc.2013.139>
89. Vadaparampil ST, Hutchins NM, Quinn GP (2013) Reproductive health in the adolescent and young adult cancer patient: an innovative training program for oncology nurses. *J Cancer Educ* 28:197–208. <https://doi.org/10.1007/s13187-012-0435-z>
90. Conflitti AC, Spaziani M, Pallotti F, Tarsitano MG, Di Nisio A, Paoli D, Lombardo F, TALENT Study Group (2023) Update on bioethical, medical and fertility issues in gender incongruence during transition age. *J Endocrinol Invest* 46:1725–1736. <https://doi.org/10.1007/s40618-023-02077-5>
91. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, Quinn G, Wallace WH, Oktay K, American Society of Clinical Oncology (2013) Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 31:2500–2510. <https://doi.org/10.1200/JCO.2013.49.2678>
92. Muller J, Sonksen J, Sommer P, Schmiegelow M, Petersen PM, Heilman C, Schmiegelow K (2000) Cryopreservation of semen from pubertal boys with cancer. *Med Pediatr Oncol* 34:191–194. [https://doi.org/10.1002/\(sici\)1096-911x\(200003\)34:33.0.co;2-q](https://doi.org/10.1002/(sici)1096-911x(200003)34:33.0.co;2-q)
93. Yee S, Fuller-Thomson E, Dwyer C, Greenblatt E, Shapiro H (2012) “Just what the doctor ordered”: factors associated with oncology patients' decision to bank sperm. *Can Urol Assoc J* 6:174. <https://doi.org/10.5489/cuaj.10084>
94. Hamilton AC, Donnelly DW, Fitzpatrick D, Coleman HG (2022) Early-onset cancers in adults: a review of epidemiology, supportive care needs and future research priorities. *Cancers* 14:4021. <https://doi.org/10.3390/cancers14164021>
95. Kanbar M, de Michele F, Giudice MG, Desmet L, Poels J, Wyns C (2021) Long-term follow-up of boys who have undergone a testicular biopsy for fertility preservation. *Hum Reprod* 36:26–39. <https://doi.org/10.1093/humrep/deaa281>
96. Galdon G, Deebeel NA, Zarandi NP, Teramoto D, Lue Y, Wang C, Swerdloff R, Pettenati MJ, Kearns WG, Howards S, Kogan S, Atala A, Sadri-Ardekani H (2022) In vitro propagation of XXY human Klinefelter spermatogonial stem cells: a step towards new fertility opportunities. *Front Endocrinol* 13:1002279. <https://doi.org/10.3389/fendo.2022.1002279>
97. Deebeel NA, Sadri-Ardekani H (2023) Fertility preservation in adolescents with Klinefelter syndrome is experimental but may increase therapeutic options for biological paternity. *Eur Urol Focus* 9:3–5. <https://doi.org/10.1016/j.euf.2022.11.007>
98. Hingu J, Galdon G, Deebeel NA, Sadri-Ardekani H (2024) Isolation and in vitro propagation of human spermatogonial stem cells (SSCs). *Methods Mol Biol* 2770:27–36. https://doi.org/10.1007/978-1-0716-3698-5_3
99. Ozimic S, Ban-Franz H, Stimpfel M (2023) Sperm cryopreservation today: approaches, efficiency, and pitfalls. *Curr Issues Mol Biol* 45:4716–4734. <https://doi.org/10.3390/cimb45060300>
100. Anderson RA, Mitchell RT, Kelsey TW, Spears N, Telfer EE, Wallace WHB (2015) Cancer treatment and gonadal function: experimental and established strategies for fertility preservation in children and young adults. *Lancet Diabetes Endocrinol* 3:556–567. [https://doi.org/10.1016/S2213-8587\(15\)00039-X](https://doi.org/10.1016/S2213-8587(15)00039-X)
101. Ginsberg JP, Carlson CA, Lin K, Hobbie WL, Wigo E, Wu X, Brinster RL, Kolon TF (2010) An experimental protocol for fertility preservation in prepubertal boys recently diagnosed with cancer: a report of acceptability and safety. *Hum Reprod* 25:37–41. <https://doi.org/10.1093/humrep/dep371>
102. Elhawary NA, AlJahdali IA, Abumansour IS, Azher ZA, Falemban AH, Madani WM, Alosaimi W, Alghamdi G, Sindi IA (2023) Phenotypic variability to medication management: an update on fragile X syndrome. *Hum Genom* 17:60–62. <https://doi.org/10.1186/s40246-023-00507-2>
103. Sun Y, Bak B, Schoenmakers N, van Trotsenburg ASP, Oostdijk W, Voshol P, Cambridge E, White JK, le Tissier P, Gharavy SNM, Martinez-Barbera JP, Stokvis-Brantsma WH, Vulsma T, Kempers MJ, Persani L, Campi I, Bonomi M, Beck-Peccoz P, Zhu H, Davis TME, Hokken-Koelega ACS, Del Blanco DG, Rangasami JJ, Ruivenkamp CAL, Laros JFJ, Kriek M, Kant SG, Bosch CAJ, Biermasz NR, Appelman-Dijkstra NM, Corssmit EP, Hovens GCJ, Pereira AM, den Dunnen JT, Wade MG, Breuning MH, Hennekam RC, Chatterjee K, Dattani MT, Wit JM, Bernard DJ (2012) Loss-of-function mutations in IGSF1 cause an X-linked syndrome of central hypothyroidism and testicular enlargement. *Nat Genet* 44:1375–1381. <https://doi.org/10.1038/ng.2453>
104. Joustra SD, Roelfsema F, Endert E, Ballieux BEPB, van Trotsenburg ASP, Fliers E, Corssmit EPM, Bernard DJ, Oostdijk W, Wit JM, Pereira AM, Biermasz NR (2016) Pituitary hormone secretion profiles in IGSF1 deficiency syndrome. *Neuroendocrinology* 103:408–416. <https://doi.org/10.1159/000439433>
105. Mendicino A, Sabbadini G, Pergola MS (2005) Clark-Baraitser syndrome: report of a new case and review of the literature. *Clin Dysmorphol* 14:133–135
106. Atkin JF, Flaitz K, Patil S, Smith W (1985) A new X-linked mental retardation syndrome. *Am J Med Genet* 21:697–705. <https://doi.org/10.1002/ajmg.1320210411>
107. Wasniewska M, Matarazzo P, Weber G, Russo G, Zampolli M, Salzano G, Zirilli G, Bertelloni S, Italian Study Group for Alterations of Gs alpha Protein Function (2006) Clinical presentation of McCune-Albright syndrome in males. *J Pediatr Endocrinol Metab* 19(Suppl 2):619–622. <https://doi.org/10.1515/jpem.2006.19.s2.619>
108. Khanna G, Kantawala K, Shinawi M, Sarwate S, Dehner LP (2010) McCune–Albright syndrome presenting with unilateral macroorchidism and bilateral testicular masses. *Pediatr Radiol* 40(Suppl 1):16. <https://doi.org/10.1007/s00247-010-1762-z>
109. Aversa T, Zirilli G, Corica D, De Luca F, Wasniewska M (2018) Phenotypic testicular abnormalities and pubertal development in boys with McCune–Albright syndrome. *Ital J Pediatr* 44:136–137. <https://doi.org/10.1186/s13052-018-0577-7>
110. Pellegrin MC, Spinelli AM, Tornese G, Barbi E (2019) Unilateral testicular enlargement in a teenager with Beckwith–Wiedemann syndrome: a case report. *Ital J Pediatr* 45:79–81. <https://doi.org/10.1186/s13052-019-0675-1>
111. Ntali G, Capatina C, Grossman A, Karavitaki N (2014) Clinical review: functioning gonadotroph adenomas. *J Clin Endocrinol Metab* 99:4423–4433. <https://doi.org/10.1210/jc.2014-2362>
112. Clemente M, Caracseghi F, Gussinyer M, Yeste D, Albusu M, Vazquez E, Ortega A, Carrascosa A (2011) Macroorchidism and panhypopituitarism: two different forms of presentation of FSH-secreting pituitary adenomas in adolescence. *Horm Res Paediatr* 75:225–230. <https://doi.org/10.1159/000322211>
113. Zadik Z, Burundukov E, Zung A (2009) Giant macroorchidism in congenital adrenal hyperplasia. *J Pediatr Endocrinol Metab* 22:1095–1097. <https://doi.org/10.1515/jpem.2009.22.12.1095>
114. Rochira V, Carani C (2009) Aromatase deficiency in men: a clinical perspective. *Nat Rev Endocrinol* 5:559–568. <https://doi.org/10.1038/nrendo.2009.176>
115. Garcia AV, Alobeid B, Traina JM, Chen SS, Weiner MA, Middleworth W (2013) Isolated primary testicular B lymphoblastic lymphoma: an unusual presentation. *J Pediatr Hematol Oncol* 35:88. <https://doi.org/10.1097/MPH.0b013e318271c470>
116. Joustra SD, van der Plas EM, Goede J, Oostdijk W, Delemarre-van de Waal HA, Hack WWM, van Buuren S, Wit JM (2015) New reference charts for testicular volume in Dutch children

- and adolescents allow the calculation of standard deviation scores. *Acta Paediatr* 104:271. <https://doi.org/10.1111/apa.12972>
117. Lachiewicz AM, Dawson DV (1994) Do young boys with fragile X syndrome have macroorchidism? *Pediatrics* 93:992–995
 118. Charalsawadi C, Wirojanan J, Jaruratanasirikul S, Ruangdaraganon N, Geater A, Limprasert P (2017) Common clinical characteristics and rare medical problems of fragile X syndrome in Thai patients and review of the literature. *Int J Pediatr* 2017:9318346. <https://doi.org/10.1155/2017/9318346>
 119. Joustra SD, Schoenmakers N, Persani L, Campi I, Bonomi M, Radetti G, Beck-Peccoz P, Zhu H, Davis TME, Sun Y, Corssmit EP, Appelman-Dijkstra NM, Heinen CA, Pereira AM, Varendijk AJ, Janssen JAMJL, Enderit E, Hennekam RC, Lombardi MP, Mannens MMAM, Bak B, Bernard DJ, Breuning MH, Chat-terjee K, Dattani MT, Oostdijk W, Biermasz NR, Wit JM, van Trotsenburg ASP (2013) The IGSF1 deficiency syndrome: characteristics of male and female patients. *J Clin Endocrinol Metab* 98:4942–4952. <https://doi.org/10.1210/jc.2013-2743>
 120. Taskinen S, Fagerholm R, Aronniemi J, Rintala R, Taskinen M (2008) Testicular tumors in children and adolescents. *J Pediatr Urol* 4:134–137. <https://doi.org/10.1016/j.jpuro.2007.10.002>
 121. Limprasert P, Jaruratanasirikul S, Vasiknanonte P (2000) Unilateral macroorchidism in fragile X syndrome. *Am J Med Genet* 95:516–517
 122. Garcia M, Barrio R, Garcia-Lavandeira M, Garcia-Rendueles AR, Escudero A, Diaz-Rodriguez E, Gorbenko Del Blanco D, Fernandez A, de Rijke YB, Vallespin E, Nevado J, Lapunzina P, Matre V, Hinkle PM, Hokken-Koelega ACS, de Miguel MP, Cameselle-Teijeiro JM, Nistal M, Alvarez CV, Moreno JC (2017) The syndrome of central hypothyroidism and macroorchidism: IGSF1 controls TRHR and FSHB expression by differential modulation of pituitary TGFbeta and Activin pathways. *Sci Rep* 7:42937. <https://doi.org/10.1038/srep42937>
 123. Tenenbaum-Rakover Y, Turgeon M, London S, Hermanns P, Pohlenz J, Bernard DJ, Bercovich D (2016) Familial central hypothyroidism caused by a novel IGSF1 gene mutation. *Thyroid* 26:1693–1700. <https://doi.org/10.1089/thy.2015.0672>
 124. Brule E, Heinen CA, Smith CL, Schang G, Li Y, Zhou X, Wang Y, Joustra SD, Wit JM, Fliers E, Repping S, van Trotsenburg ASP, Bernard DJ (2021) IGSF1 does not regulate spermatogenesis or modify FSH synthesis in response to inhibins or activins. *J Endocr Soc* 5:vbv023. <https://doi.org/10.1210/jendso/vbv023>
 125. Persani L, Brabant G, Dattani M, Bonomi M, Feldt-Rasmussen U, Fliers E, Gruters A, Maiter D, Schoenmakers N, van Trotsenburg ASP (2018) 2018 European thyroid association (ETA) guidelines on the diagnosis and management of central hypothyroidism. *Eur Thyroid J* 7:225–237. <https://doi.org/10.1159/000491388>
 126. Patrikidou A, Cazzaniga W, Berney D, Boormans J, de Angst I, Di Nardo D, Fankhauser C, Fischer S, Gravina C, Gremmels H, Heidenreich A, Janisch F, Leao R, Nicolai N, Oing C, Oldenburg J, Shepherd R, Tandstad T, Nicol D (2023) European association of urology guidelines on testicular cancer: 2023 update. *Eur Urol* 84:289–301. <https://doi.org/10.1016/j.eururo.2023.04.010>
 127. Latronico AC, Brito VN, Carel J (2016) Causes, diagnosis, and treatment of central precocious puberty. *Lancet Diabetes Endocrinol* 4:265–274. [https://doi.org/10.1016/S2213-8587\(15\)00380-0](https://doi.org/10.1016/S2213-8587(15)00380-0)
 128. Partsch CJ, Sippell WG (2001) Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens. *Hum Reprod Update* 7:292–302. <https://doi.org/10.1093/humupd/7.3.292>
 129. Soriano-Guillen L, Corripio R, Labarta JJ, Canete R, Castro-Feijoo L, Espino R, Argente J (2010) Central precocious puberty in children living in Spain: incidence, prevalence, and influence of adoption and immigration. *J Clin Endocrinol Metab* 95:4305–4313. <https://doi.org/10.1210/jc.2010-1025>
 130. Brunner HG, Otten BJ (1999) Precocious puberty in boys. *N Engl J Med* 341:1763–1765. <https://doi.org/10.1056/NEJM199912023412311>
 131. Aguirre RS, Eugster EA (2018) Central precocious puberty: from genetics to treatment. *Best Pract Res Clin Endocrinol Metab* 32:343–354. <https://doi.org/10.1016/j.beem.2018.05.008>
 132. Brito VN, Canton APM, Seraphim CE, Abreu AP, Macedo DB, Mendonca BB, Kaiser UB, Argente J, Latronico AC (2023) The congenital and acquired mechanisms implicated in the etiology of central precocious puberty. *Endocr Rev* 44:193–221. <https://doi.org/10.1210/edrv/bnac020>
 133. Eugster EA (2009) Peripheral precocious puberty: causes and current management. *Horm Res* 71(Suppl 1):64–67. <https://doi.org/10.1159/000178041>
 134. Spadoni GL, Cianfarani S (2010) Bone age assessment in the workup of children with endocrine disorders. *Horm Res Paediatr* 73:2–5. <https://doi.org/10.1159/000271910>
 135. Cheuiche AV, da Silveira LG, de Paula LCP, Lucena IRS, Silveiro SP (2021) Diagnosis and management of precocious sexual maturation: an updated review. *Eur J Pediatr* 180:3073–3087. <https://doi.org/10.1007/s00431-021-04022-1>
 136. Carel J, Leger J (2008) Clinical practice. Precocious puberty. *N Engl J Med* 358:2366–2377. <https://doi.org/10.1056/NEJMc0800459>
 137. Pasternak Y, Friger M, Loewenthal N, Haim A, Hershkovitz E (2012) The utility of basal serum LH in prediction of central precocious puberty in girls. *Eur J Endocrinol* 166:295–299. <https://doi.org/10.1530/EJE-11-0720>
 138. Auer MK, Nordenstrom A, Lajic S, Reisch N (2023) Congenital adrenal hyperplasia. *Lancet* 401:227–244. [https://doi.org/10.1016/S0140-6736\(22\)01330-7](https://doi.org/10.1016/S0140-6736(22)01330-7)
 139. Carel J, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, ESPERLWPES GnRH Analogs Consensus Conference Group, Antoniazzi F, Berenbaum S, Bourguignon J, Chrousos GP, Coste J, Deal S, de Vries L, Foster C, Heger S, Holland J, Jahnkainen K, Juul A, Kaplowitz P, Lahlou N, Lee MM, Lee P, Merke DP, Neely EK, Oostdijk W, Phillip M, Rosenfield RL, Shulman D, Styne D, Tauber M, Wit JM (2009) Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* 123:752. <https://doi.org/10.1542/peds.2008-1783>
 140. Bangalore Krishna K, Fuqua JS, Rogol AD, Klein KO, Popovic J, Houk CP, Charmandari E, Lee PA, Freire AV,ROPelato MG, Yazid Jalaludin M, Mbogo J, Kanaka-Gantenbein C, Luo X, Eugster EA, Klein KO, Vogiatzi MG, Reifschneider K, Bamba V, Garcia Rudaz C, Kaplowitz P, Backeljauw P, Allen DB, Palmert MR, Harrington J, Guerra-Junior G, Stanley T, Torres Tamayo M, Miranda Lora AL, Bajpai A, Silverman LA, Miller BS, Dayal A, Horikawa R, Oberfield S, Rogol AD, Tajima T, Popovic J, Witchel SF, Rosenthal SM, Finlayson C, Hannema SE, Castilla-Peon MF, Mericq V, Medina Bravo PG (2019) Use of gonadotropin-releasing hormone analogs in children: update by an international consortium. *Horm Res Paediatr* 91:357–372. <https://doi.org/10.1159/000501336>
 141. Guaraldi F, Beccuti G, Gori D, Ghizzoni L (2016) Management of endocrine disease: long-term outcomes of the treatment of central precocious puberty. *Eur J Endocrinol* 174:79. <https://doi.org/10.1530/EJE-15-0590>
 142. Haddad NG, Eugster EA (2019) Peripheral precocious puberty including congenital adrenal hyperplasia: causes, consequences, management and outcomes. *Best Pract Res Clin Endocrinol Metab* 33:101273. <https://doi.org/10.1016/j.beem.2019.04.007>
 143. Fuqua JS, Eugster EA (2024) Presentation and care for children with peripheral precocious puberty. *Endocrinol Metab Clin North Am* 53:251–265. <https://doi.org/10.1016/j.ecl.2024.01.006>

144. Boehm U, Bouloux P, Dattani MT, de Roux N, Dode C, Dunkel L, Dwyer AA, Giacobini P, Hardelin J, Juul A, Maghnie M, Pitteloud N, Prevot V, Raivio T, Tena-Sempere M, Quinton R, Young J (2015) Expert consensus document: european consensus statement on congenital hypogonadotropic hypogonadism—pathogenesis, diagnosis and treatment. *Nat Rev Endocrinol* 11:547–564. <https://doi.org/10.1038/nrendo.2015.112>
145. Cheng HL, Harris SR, Sritharan M, Behan MJ, Medlow SD, Steinbeck KS (2020) The tempo of puberty and its relationship to adolescent health and well-being: a systematic review. *Acta Paediatr* 109:900–913. <https://doi.org/10.1111/apa.15092>
146. Abitbol L, Zborovski S, Palmert MR (2016) Evaluation of delayed puberty: what diagnostic tests should be performed in the seemingly otherwise well adolescent? *Arch Dis Child* 101:767–771. <https://doi.org/10.1136/archdischild-2015-310375>
147. Lee PA (1980) Normal ages of pubertal events among American males and females. *J Adolesc Health Care* 1:26–29. [https://doi.org/10.1016/s0197-0070\(80\)80005-2](https://doi.org/10.1016/s0197-0070(80)80005-2)
148. Sedlmeyer IL, Palmert MR (2002) Delayed puberty: analysis of a large case series from an academic center. *J Clin Endocrinol Metab* 87:1613–1620. <https://doi.org/10.1210/jcem.87.4.8395>
149. Lawaetz JG, Hagen CP, Mieritz MG, Blomberg Jensen M, Petersen JH, Juul A (2015) Evaluation of 451 Danish boys with delayed puberty: diagnostic use of a new puberty nomogram and effects of oral testosterone therapy. *J Clin Endocrinol Metab* 100:1376–1385. <https://doi.org/10.1210/jc.2014-3631>
150. Howard SR, Quinton R (2023) Outcomes and experiences of adults with congenital hypogonadism can inform improvements in the management of delayed puberty. *J Pediatr Endocrinol Metab* 37:1–7. <https://doi.org/10.1515/jpem-2023-0407>
151. Aung Y, Kokotsis V, Yin KN, Banerjee K, Butler G, Dattani MT, Dimitri P, Dunkel L, Hughes C, McGuigan M, Korbonits M, Palatoglou G, Sakka S, Shah P, Storr HL, Willemsen RH, Howard SR (2023) Key features of puberty onset and progression can help distinguish self-limited delayed puberty from congenital hypogonadotropic hypogonadism. *Front Endocrinol* 14:1226839. <https://doi.org/10.3389/fendo.2023.1226839>
152. Bollino A, Cangiano B, Goggi G, Federici S, Duminuco P, Giovanelli L, Galazzi E, Vezzoli V, Persani L, Bonomi M (2020) Pubertal delay: the challenge of a timely differential diagnosis between congenital hypogonadotropic hypogonadism and constitutional delay of growth and puberty. *Minerva Pediatr* 72:278–287. <https://doi.org/10.23736/S0026-4946.20.05860-0>
153. Esquivel-Zuniga R, Rogol AD (2023) Functional hypogonadism in adolescence: an overlooked cause of secondary hypogonadism. *Endocr Connect* 12:e230190. <https://doi.org/10.1530/EC-0190>
154. Bonomi M, Vezzoli V, Krausz C, Guizzardi F, Vezzani S, Simoni M, Bassi I, Duminuco P, Di Iorgi N, Giavoli C, Pizzocaro A, Russo G, Moro M, Fatti L, Ferlin A, Mazzanti L, Zatelli MC, Cannavo S, Isidori AM, Pincelli AI, Prodam F, Mancini A, Limone P, Tanda ML, Gaudino R, Salerno M, Francesca P, Maghnie M, Maggi M, Persani L, Italian Network on Central Hypogonadism, Italian Network on Central Hypogonadism (NICe group) (2018) Characteristics of a nationwide cohort of patients presenting with isolated hypogonadotropic hypogonadism (IHH). *Eur J Endocrinol* 178:23–32. <https://doi.org/10.1530/EJE-17-0065>
155. Vezzoli V, Hrvat F, Goggi G, Federici S, Cangiano B, Quinton R, Persani L, Bonomi M (2023) Genetic architecture of self-limited delayed puberty and congenital hypogonadotropic hypogonadism. *Front Endocrinol* 13:1069741. <https://doi.org/10.3389/fendo.2022.1069741>
156. Grinspon RP, Bergada I, Rey RA (2020) Male hypogonadism and disorders of sex development. *Front Endocrinol* 11:211. <https://doi.org/10.3389/fendo.2020.00211>
157. Bonomi M, Libri DV, Guizzardi F, Guarducci E, Maiolo E, Pignatti E, Asci R, Persani L, Idiopathic Central Hypogonadism Study Group of the Italian Societies of Endocrinology and Pediatric Endocrinology and Diabetes (2012) New understandings of the genetic basis of isolated idiopathic central hypogonadism. *Asian J Androl* 14:49–56. <https://doi.org/10.1038/aja.2011.68>
158. Palmert MR, Dunkel L (2012) Clinical practice. Delayed puberty. *N Engl J Med* 366:443–453. <https://doi.org/10.1056/NEJMc p1109290>
159. Marshall WA, Tanner JM (1970) Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 45:13–23. <https://doi.org/10.1136/adc.45.239.13>
160. Dwyer AA, Phan-Hug F, Hauschild M, Elowe-Gruau E, Pitteloud N (2015) Transition in endocrinology: hypogonadism in adolescence. *Eur J Endocrinol* 173:15. <https://doi.org/10.1530/EJE-14-0947>
161. Zhu J, Choa RE, Guo MH, Plummer L, Buck C, Palmert MR, Hirschhorn JN, Seminara SB, Chan Y (2015) A shared genetic basis for self-limited delayed puberty and idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 100:646. <https://doi.org/10.1210/jc.2015-1080>
162. Dunkel L, Quinton R (2014) Transition in endocrinology: induction of puberty. *Eur J Endocrinol* 170:229. <https://doi.org/10.1530/EJE-13-0894>
163. Varimo T, Miettinen PJ, Kansakoski J, Raivio T, Hero M (2017) Congenital hypogonadotropic hypogonadism, functional hypogonadotropism or constitutional delay of growth and puberty? An analysis of a large patient series from a single tertiary center. *Hum Reprod* 32:147–153. <https://doi.org/10.1093/humrep/dew294>
164. Persani L, Bonomi M, Cools M, Dattani M, Dunkel L, Gravholt CH, Juul A (2021) ENDO-ERN expert opinion on the differential diagnosis of pubertal delay. *Endocrine* 71:681–688. <https://doi.org/10.1007/s12020-021-02626-z>
165. Howard SR, Dunkel L (2018) Management of hypogonadism from birth to adolescence. *Best Pract Res Clin Endocrinol Metab* 32:355–372. <https://doi.org/10.1016/j.beem.2018.05.011>
166. Albrethsen J, Johannsen TH, Jorgensen N, Frederiksen H, Senels HP, Jorgensen HL, Fahrenkrug J, Petersen JH, Linneberg A, Nordkap L, Bang AK, Andersson A, Juul A (2020) Evaluation of serum insulin-like factor 3 quantification by LC-MS/MS as a biomarker of leydig cell function. *J Clin Endocrinol Metab* 105:dgaal45. <https://doi.org/10.1210/clinem/dgaal45.10.1210/clinem/dgaal45>
167. Ljubicic ML, Jespersen K, Akglaede L, Hagen CP, Petersen JH, Andersen HR, Linneberg A, Main KM, Andersson A, Johannsen TH, Juul A (2020) The LH/FSH ratio is not a sex-dimorphic marker after infancy: data from 6417 healthy individuals and 125 patients with differences of sex development. *Hum Reprod* 35:2323–2335. <https://doi.org/10.1093/humrep/deaa182>
168. Resende EAMR, Lara BHJ, Reis JD, Ferreira BP, Pereira GA, Borges MF (2007) Assessment of basal and gonadotropin-releasing hormone-stimulated gonadotropins by immunochemiluminometric and immunofluorometric assays in normal children. *J Clin Endocrinol Metab* 92:1424–1429. <https://doi.org/10.1210/jc.2006-1569>
169. Wu FC, Brown DC, Butler GE, Stirling HF, Kelnar CJ (1993) Early morning plasma testosterone is an accurate predictor of imminent pubertal development in prepubertal boys. *J Clin Endocrinol Metab* 76:26–31. <https://doi.org/10.1210/jcem.76.1.8421096>
170. Neely EK, Hintz RL, Wilson DM, Lee PA, Gautier T, Argente J, Stene M (1995) Normal ranges for immunochemiluminometric gonadotropin assays. *J Pediatr* 127:40–46. [https://doi.org/10.1016/s0022-3476\(95\)70254-7](https://doi.org/10.1016/s0022-3476(95)70254-7)

171. Grinspon RP, Ropelato MG, Gottlieb S, Keselman A, Martinez A, Ballerini MG, Domene HM, Rey RA (2010) Basal follicle-stimulating hormone and peak gonadotropin levels after gonadotropin-releasing hormone infusion show high diagnostic accuracy in boys with suspicion of hypogonadotropic hypogonadism. *J Clin Endocrinol Metab* 95:2811–2818. <https://doi.org/10.1210/jc.2009-2732>
172. Growth Hormone Research Society (2000) Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. *J Clin Endocrinol Metab* 85:3990–3993. <https://doi.org/10.1210/jcem.85.11.6984>
173. Hage C, Gan H, Ibba A, Patti G, Dattani M, Loche S, Maghnie M, Salvatori R (2021) Advances in differential diagnosis and management of growth hormone deficiency in children. *Nat Rev Endocrinol* 17:608–624. <https://doi.org/10.1038/s41574-021-00539-5>
174. Galazzi E, Improda N, Cerbone M, Soranna D, Moro M, Fatti LM, Zambon A, Bonomi M, Salerno M, Dattani M, Persani L (2021) Clinical benefits of sex steroids given as a priming prior to GH provocative test or as a growth-promoting therapy in peripubertal growth delays: results of a retrospective study among ENDO-ERN centres. *Clin Endocrinol (Oxf)* 94:219–228. <https://doi.org/10.1111/cen.14337>
175. Tenuta M, Carlomagno F, Cangiano B, Kanakis G, Pozza C, Sbardella E, Isidori AM, Krausz C, Gianfrilli D (2021) Somatotrophic-testicular axis: a crosstalk between GH/IGF-I and gonadal hormones during development, transition, and adult age. *Andrology* 9:168–184. <https://doi.org/10.1111/andr.12918>
176. Murray PG, Dattani MT, Clayton PE (2016) Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. *Arch Dis Child* 101:96–100. <https://doi.org/10.1136/archdischild-2014-307228>
177. Wetterau LA (2012) The pros and cons of sex steroid priming in growth hormone stimulation testing. *J Pediatr Endocrinol Metab* 25:1049–1055. <https://doi.org/10.1515/jpem.2011.327>
178. Lazar L, Phillip M (2010) Is sex hormone priming in peripubertal children prior to growth hormone stimulation tests still appropriate? *Horm Res Paediatr* 73:299–302. <https://doi.org/10.1159/000284396>
179. Saengkaew T, Patel HR, Banerjee K, Butler G, Dattani MT, McGuigan M, Storr HL, Willemsen RH, Dunkel L, Howard SR (2021) Genetic evaluation supports differential diagnosis in adolescent patients with delayed puberty. *Eur J Endocrinol* 185:617–627. <https://doi.org/10.1530/EJE-21-0387>
180. Lippincott MF, Schafer EC, Hindman AA, He W, Brauner R, Delaney A, Grinspon R, Hall JE, Hirschhorn JN, McElreavey K, Palmert MR, Rey R, Seminara SB, Salem RM, Chan Y, Delayed Puberty Genetics Consortium (2024) Contributions of common genetic variants to constitutional delay of puberty and idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab*. <https://doi.org/10.1210/clinem/dgae166>
181. Pozo J, Argente J (2003) Ascertainment and treatment of delayed puberty. *Horm Res* 60(Suppl 3):35–48. <https://doi.org/10.1159/000074498>
182. Zachmann M, Studer S, Prader A (1987) Short-term testosterone treatment at bone age of 12 to 13 years does not reduce adult height in boys with constitutional delay of growth and adolescence. *Helv Paediatr Acta* 42:21–28
183. Zachmann M (1991) Therapeutic indications for delayed puberty and hypogonadism in adolescent boys. *Horm Res* 36:141–146. <https://doi.org/10.1159/000182148>
184. Nordenstrom A, Ahmed SF, van den Akker E, Blair J, Bonomi M, Brachet C, Broersen LHA, Claahsen-van der Grinten HL, Dessens AB, Gawlik A, Gravholt CH, Juul A, Krausz C, Raivio T, Smyth A, Touraine P, Vitali D, Dekkers OM (2022) Pubertal induction and transition to adult sex hormone replacement in patients with congenital pituitary or gonadal reproductive hormone deficiency: an Endo-ERN clinical practice guideline. *Eur J Endocrinol* 186:G9–G49. <https://doi.org/10.1530/EJE-22-0073>
185. Stancampiano MR, Lucas-Herald AK, Russo G, Rogol AD, Ahmed SF (2019) Testosterone therapy in adolescent boys: the need for a structured approach. *Horm Res Paediatr* 92:215–228. <https://doi.org/10.1159/000504670>
186. Federici S, Goggi G, Quinton R, Giovanelli L, Persani L, Cangiano B, Bonomi M (2022) New and consolidated therapeutic options for pubertal induction in hypogonadism: in-depth review of the literature. *Endocr Rev* 43:824–851. <https://doi.org/10.1210/endrev/bnab043>
187. Cangiano B, Goggi G, Federici S, Bresesti C, Cotellessa L, Guizzardi F, Vezzoli V, Duminuco P, Persani L, Bonomi M (2021) Predictors of reproductive and non-reproductive outcomes of gonadotropin mediated pubertal induction in male patients with congenital hypogonadotropic hypogonadism (CHH). *J Endocrinol Invest* 44:2445–2454. <https://doi.org/10.1007/s40618-021-01556-x>
188. Rosenfeld RG, Northcraft GB, Hintz RL (1982) A prospective, randomized study of testosterone treatment of constitutional delay of growth and development in male adolescents. *Pediatrics* 69:681–687
189. Soliman AT, Khadir MM, Asfour M (1995) Testosterone treatment in adolescent boys with constitutional delay of growth and development. *Metabolism* 44:1013–1015. [https://doi.org/10.1016/0026-0495\(95\)90098-5](https://doi.org/10.1016/0026-0495(95)90098-5)
190. Albanese A, Stanhope R (1995) Predictive factors in the determination of final height in boys with constitutional delay of growth and puberty. *J Pediatr* 126:545–550. [https://doi.org/10.1016/s0022-3476\(95\)70347-0](https://doi.org/10.1016/s0022-3476(95)70347-0)
191. Richman RA, Kirsch LR (1988) Testosterone treatment in adolescent boys with constitutional delay in growth and development. *N Engl J Med* 319:1563–1567. <https://doi.org/10.1056/NEJM198812153192402>
192. Gilsanz V, Chalfant J, Kalkwarf H, Zemel B, Lappe J, Oberfield S, Shepherd J, Wren T, Winer K (2011) Age at onset of puberty predicts bone mass in young adulthood. *J Pediatr* 158:100–102. <https://doi.org/10.1016/j.jpeds.2010.06.054>

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

Authors and Affiliations

M. Bonomi^{1,2}  · B. Cangiano^{1,2} · S. Cianfarani^{3,4,5} · A. Garolla⁶ · D. Gianfrilli^{7,8} · F. Lanfranco⁹ · G. Rastrelli¹⁰ · E. Sbardella^{7,8} · G. Corona¹¹ · A. M. Isidori^{7,8} · V. Rochira^{12,13} 

✉ M. Bonomi
m.bonomi@auxologico.it

✉ V. Rochira
vincenzo.rochira@unimore.it

¹ Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy

² Department of Endocrine and Metabolic Diseases, IRCCS Istituto Auxologico Italiano, Piazzale Brescia 20, 20149 Milan, Italy

³ Endocrinology and Diabetes Unit, Bambino Gesù Children's Hospital, Rome, Italy

⁴ Department of Systems Medicine, University of Rome "Tor Vergata", Rome, Italy

⁵ Department of Women's and Children's Health, Karolinska Institute, Stockholm, Sweden

⁶ Unit of Andrology and Reproductive Medicine, Department of Medicine, University of Padova, Padua, Italy

⁷ Section of Medical Pathophysiology and Endocrinology, Department of Experimental Medicine, "Sapienza" University of Rome, Rome, Italy

⁸ Centre for Rare Diseases (Endo-ERN Accredited), Policlinico Umberto I, Rome, Italy

⁹ Division of Endocrinology, Andrology and Metabolism, Department of Medical Sciences, Humanitas Gradenigo, University of Turin, Turin, Italy

¹⁰ Department of Experimental and Clinical Biomedical Sciences "Mario Serio", Careggi Hospital, University of Florence, Florence, Italy

¹¹ Endocrinology Unit, Medical Department, Maggiore-Bellaria Hospital, Azienda Usl, Bologna, Italy

¹² Endocrinology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

¹³ Unit of Endocrinology, Department of Medical Specialties, Azienda Ospedaliero-Universitaria Di Modena Policlinico Di Modena, Ospedale Civile Di Baggiovara, Via Giardini 1355, 41126 Modena, Italy