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Etiology and Treatment of Hypogonadism in Adolescents

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Factors that mitigate the onset of puberty have yet to be fully elucidated. Gonadarche refers to the onset of gonadal sex steroid production during puberty. Gonadarche results from pulsatile gonadotropin releasing hormone (GnRH) secretion from the hypothalamus. GnRH secretion occurs every 60 to 90 minutes,[1] and there is subsequent release of the pituitary gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH) initially during sleep,[2] which leads to gonadal stimulation. LH stimulates Leydig cell hyperplasia in males and subsequent testosterone release. FSH has little effect in males until the onset of spermarche (sperm maturation). In females, FSH stimulates the production of estradiol via ovarian follicular development. Testosterone and estradiol secretion lead to the development of secondary sexual characteristics. Adequate functioning at all levels of the hypothalamic-pituitary-gonadal axis is necessary for normal gonadal development and subsequent sex steroid production. Deficiencies at any level of the axis can lead to a hypogonadal state.

In boys, hypogonadism can manifest as a complete lack of secondary sexual development or failure of normal pubertal progression. In girls, it can present with failure of pubertal initiation, failure of pubertal progression, or menstrual irregularities. Abnormalities within the hypothalamus or pituitary lead to *hypogonadotropic hypogonadism* whereas primary gonadal failure is characterized as *hypergonadotropic hypogonadism*.

HYPOGONADOTROPIC HYPOGONADISM

Hypogonadotropic hypogonadism can be attributed to a variety of congenital origins including single gene mutations, idiopathic forms, and genetic syndromes. Acquired causes of hypogonadotropic hypogonadism include central nervous system (CNS) insults such as trauma, irradiation, and intracranial tumors. By far the most common cause of hypogonadotropic hypogonadism is transient, and is termed constitutional delay of growth and puberty (CDGP). Each of these causes is briefly discussed here, and the molecular genetic causes of hypogonadotropic hypogonadism are shown in Table 1.

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Constitutional Delay of Growth and Puberty

CDGP is a variation of normal development that can be difficult to differentiate from pathologic hypogonadotropic hypogonadism. In this condition, puberty and the pubertal growth spurt occur at or later than the extreme upper end of the normal age. The diagnosis is made more often in boys than girls, likely due to referral bias, and has a strongly familial pattern.[3] Skeletal maturation is delayed in comparison with chronologic age. CDGP results in delayed but *normal* puberty; thus puberty progresses through the normal stages but starts at a later time. Children with CDGP achieve their genetic potential for height,[4] and laboratory evaluation is normal. Some patients benefit from short-term treatment to augment secondary sexual development and boost linear growth.[5]

Congenital Origins

Gene defects

Nuclear receptor mutations: Nuclear receptors influence gene transcription at multiple levels, and exert their effects in a time- and dosage-specific fashion. An important nuclear receptor involved in gonadotropin secretion is steroidogenic factor-1 (SF-1), a key regulator of genes involved in sexual differentiation, steroidogenesis, and reproduction. SF-1 knockout mice show marked abnormalities in the development of the hypothalamus and impaired development of pituitary gonadotropes, with decreased levels of serum gonadotropins as well as gonadal dysgenesis.[6] Target genes of SF-1 within the hypothalamus and pituitary include the gonadotropin releasing hormone receptor (GnRHR) and the β subunit of LH. Both heterozygous and homozygous mutations in the DNA binding domain of SF-1 result in complete XY sex reversal, testicular dysgenesis, and adrenal failure in genotypic males. A milder phenotype has also been described in which there is impaired gonadal but intact adrenal function.[7] In a genetic female, a heterozygous SF-1 mutation has been associated with primary adrenal failure but normal ovarian development.[8] Thus, SF-1 mutations exist within a broad clinical spectrum that will undoubtedly continue to expand.

DAX-1 is an orphan nuclear receptor that is involved in steroidogenesis and functions as a repressor of SF-1 mediated transcription. Mutations have been identified in *NROB1*, the gene that encodes DAX1, on the Xp21 locus. Males with DAX1 mutations typically present with early-onset adrenal insufficiency and subsequent delayed puberty secondary to hypogonadotropic hypogonadism.[9] However, a delayed presentation of primary adrenal insufficiency has also been reported.[10] DAX1 mutations can lead to both hypothalamic and pituitary dysfunction with decreased GnRH and gonadotropin secretion.[11] DAX1 mutations can also cause defects in spermatogenesis, and in one study affected males also had evidence of azospermia.[12] Therefore, mutations in DAX-1, as in SF-1, can lead to the development of hypogonadism in a multitude of ways.

Kallman syndrome: Impairment of GnRH secretion can also occur from defects in migration of GnRH producing neurons. Kallman syndrome (KS) refers to the combination of hypogonadotropic hypogonadism and anosmia. The X-linked form results from a defect in the migration of GnRH and olfactory neurons due to a mutation in the *KAL1* gene. This gene encodes for anosmin-1, a glycoprotein essential for neuronal migration and growth.[13] Individuals with KS also have aplasia of the olfactory bulb as noted on magnetic resonance

imaging (MRI).[14] Although *KAL1* gene defects have been the prototype of KS, there is emerging evidence that autosomal forms may be more prevalent than previously thought. In one study, *KAL1* gene defects accounted for only 14% of cases with familial KS. Mutations in unidentified autosomal genes were postulated to cause the remainder. Subjects with presumed autosomal gene defects had some response to GnRH pulses, indicating partial preservation of hypothalamic GnRH-secreting neurons, though still with phenotypic similarity to the X-linked version of the syndrome.[15] Fibroblast growth receptor 1 (FGFR1) mutations may account for as many as 10% of cases,[16] and mutations in the prokineticin 2 (PROK2) gene have also been identified in individuals with KS and normosmic hypogonadotropic hypogo-nadism.[17] No matter what the underlying molecular genetic cause, lack of adequate GnRH secretion leads to decreased circulating gonadotropins in both autosomal and X-linked cases.

Isolated hypogonadotropic hypogonadism: Isolated hypogonadotropic hypogonadism (IHH) refers to cases in which anosmia is absent. One potential cause is loss of function mutations of the GnRHR, a G-protein coupled receptor. At least 8 mutations of the GnRHR in 7 families have been identified. Notable genotype-phenotype variation exists even within members of the same kindred due to incomplete activation of GnRHR function.[18] Males with these mutations display signs of hypogonadism and small testes. Females typically present with primary amenorrhea.[19] Another important cause of IHH has been traced to mutations in GPR54, which has a critical role in hypothalamic GnRH signaling and release.[20] Of note, both KS and IHH may be found in the same kindred. IHH has also been noted to be reversible in some patients.[21]

Transcription factor mutations: Even with intact GnRH production and signal transduction, pituitary gonadotropin synthesis may still be deficient due to mutations in a variety of transcription factors. An important transcription factor involved in the developmental cascade of pituitary gonadotrope cells is Prop-1. Prop-1 is the prophet of the pituitary transcription factor Pit 1, a paired-like homeodomain transcription factor that is responsible for early embryonic pituitary development. Prop-1 gene mutations can result in familial combined pituitary hormone deficiency including growth hormone deficiency, central hypothyroidism, and hypogonadotropic hypogonadism.[22] In one analysis of 8 members of a consanguineous family with Prop-1 gene mutations, all 8 family members had gonadotropin deficiency and failure of spontaneous sexual maturation.[23] There is also a variable pattern of phenotypic expressivity associated with Prop-1 mutations, with different deficiencies appearing at different time periods within the same family.

Like Prop-1, the transcription factor HESX1 is needed for normal pituitary development.[24] Deficiencies in HESX1, initially identified in 1998, are a rare cause of septo-optic dysplasia[25] which may be associated with hypogonadotropic hypogonadism.[26] Other transcription factors implicated in rare cases of hypogonadotropic hypogonadism include LHX4[27] and SOX 2.[28] All patients with hypopituitarism, including idiopathic forms, are at risk for hypogonadotropic hypogonadism.

Leptin and leptin receptor defects: Congenital leptin deficiency results from loss of function mutations of the *LEP* gene, which encodes for the leptin protein. Leptin interacts

with the leptin receptor, a member of the interleukin-6 family of receptors. This interaction stimulates the Jak-Stat pathway and leads to activation of downstream target genes. Leptin deficiency acts as a sign of nutritional deprivation and results in the suppression of the reproductive axis. Classic findings in individuals with leptin deficiency include hyperphagia, obesity, and hypogonadotropic hypogonadism. Administration of leptin seemingly rectifies these abnormalities.[29] Leptin receptor (LEPR) abnormalities have a similar phenotype to congenital leptin deficiency. Females with this mutation have hypogonadotropic hypogonadism. These girls present with delayed puberty, lack of a pubertal growth spurt, and reduced expression of secondary sexual characteristics. Some may have irregular menses due to aromatization of subcutaneous fat to estrogen, which then stimulates uterine hyperplasia. Males with leptin receptor mutations have hypogonadotropic hypogonadism and diminished testosterone production.[30]

Syndromes—Numerous syndromes include neuroendocrine dysfunction as a potential feature. Perhaps the best known is Prader-Willi syndrome (PWS), which is caused by a genetic defect involving paternal chromosome 15, usually in the form of a microdeletion within the long arm or maternal unipaternal disomy.[31] Hypothalamic dysfunction is marked in these patients as evidenced by their hypotonia, hyperphagia, and intermittent temperature instability. The hypothalamic dysfunction also leads to hypogonadism and may be attributed to an absence of or abnormal location of GnRH neurons. Early studies in individuals with PWS revealed low circulating serum gonadotropins and in males, attenuated testosterone response to human chorionic gonadotropin.[32] Physical findings in boys include micropenis, scrotal hypoplasia, cryptorchidism, and small testes. Either absent or delayed puberty may ensue. In girls, findings may be less remarkable and include hypoplasia of the clitoris or labia minora, primary amenorrhea, and delayed puberty.[33] However, a wide spectrum of hypogonadism exists in PWS, with some women achieving fertility without hormone replacement therapy.[34,35]

Acquired Origins

Any significant CNS insult can result in acquired hypogonadotropic hypogonadism. Two of the most common causes in children are traumatic brain injury and CNS tumors.

Traumatic brain injury—Traumatic brain injury (TBI) is an insult to the brain that results in neurologic dysfunction. TBI can have significant neurocognitive, neuropsychological, and neuroendocrine sequelae.[36,37] Anterior pituitary insufficiency resulting from TBI has been noted in the past, but is garnering more attention as a high prevalence of pituitary hormone insufficiency has been demonstrated.[38] Some retrospective studies indicate that gonadotropin deficiency may be found in 90% to 95% of those with history of TBI,[39] although prospective studies in adults have noted the prevalence to be far less. In one study, hormonal evaluation was conducted on TBI patients at baseline (acute phase) and at 12 months. In the acute phase, approximately 42% of those evaluated had gonadotropin deficiency. At the 12-month follow-up, many of these patients spontaneously recovered reproductive function. The final prevalence of hypogonadism was 7.7%.[40] It is clear that all patients with a history of TBI require ongoing surveillance for pituitary problems, including hypogonadotropic hypogonadism.

Central nervous system tumors—Intracranial injury can also occur as a result of CNS tumors. In children, resultant hypogonadotropic hypogonadism can exist as a result of the primary tumor or due to the therapeutic regimen needed to treat the lesion. In a prospective study of 75 children with various CNS tumors, 13% had an abnormality in gonadotropin secretion before initiation of therapy.[41] In a retrospective study focusing on craniopharyngioma, only 1 out of 64 patients had evidence of hypogonadism before treatment. However, after surgical resection and adjuvant radiotherapy, 80% of those evaluated at a pubertal age had evidence of hypogonadism.[42] Gonadotropin deficiency and delayed puberty are most likely in those who receive 40 Gy or more of radiation.[43] Gonadotropin deficiency may continue to evolve for many years after irradiation, with rates of total incidence ranging from 20% to 50%.[44,45] Therefore, all children who have CNS lesions should be monitored for gonadotropin deficiency and signs of pubertal delay.[46]

Hypothalamic amenorrhea—Hypothalamic amenorrhea is commonly associated with eating disorders such as anorexia nervosa, and also occurs in elite female athletes. Clinical manifestations include absence of menstrual cycles, increased exercise, and weight loss. In these girls, suppression of GnRH secretion results in attenuation of LH and FSH release, and decreased estrogen production.[47] Several theories have been postulated for this hypothalamic dysfunction, including low circulating energy levels due to high energy expenditure and relative deficiency of nutritional intake.[47] Girls with hypothalamic amenorrhea also have low circulating leptin levels. Administration of recombinant leptin to some women with hypothalamic amenorrhea leads to elevated LH and estradiol, resulting in follicular growth and ovulation.[48]

HYPERGONADOTROPIC HYPOGONADISM

Primary hypogonadism can be due to congenital origins such as chromosomal abnormalities, syndromes, or genetic mutations. Primary hypogonadism can also be acquired later in childhood or adolescence due to autoimmunity or exposure to chemotherapy or radiation. Alterations in gonadotropins, the gonadotropin receptors, or within the gonads themselves can lead to hypogonadism with decreased testosterone and estradiol secretion. The decreased sex steroid secretion causes increased production of gonadotropins manifesting as hypergonadotropic hypogonadism. Congenital causes of primary hypogonadism are outlined in Table 2.

Congenital Origins

The most common cause of congenital primary hypogonadism is sex chromosome aneuploidy as is present in Turner syndrome and Klinefelter syndrome. Isolated abnormalities of the X chromosome are also associated with primary ovarian failure.

Turner syndrome—Turner syndrome (TS) occurs in 1 in 2500 live born females.[49] Diagnosis of the syndrome requires the combination of characteristic physical features, including short stature as well as partial or complete absence of an X chromosome.[50] More than half of girls with TS have chromosomal mosaicism. Approximately 30% will begin puberty spontaneously, but only a small minority will progress to menarche.[51] Spontaneous pregnancy has been reported but is extremely rare in this population.[52] Although initially

intrinsically normal, the ovaries in girls with TS undergo accelerated atresia such that ovarian failure is often already present and may be detected at birth. Precisely which genes on the X chromosome are necessary for ovarian maintenance is unknown. FSH levels during early life have been found to be significantly lower in girls with mosaic TS as compared with those who are monosomic.[53]

Klinefelter syndrome—Klinefelter syndrome is the most common congenital cause of primary hypogonadism and occurs in 1 in 1000 live male births.[54] The most common genotype is XXY, although variants exist with different numbers of X chromosomes. Tall stature, a eunuchoid body habitus, gynecomastia, and small, firm testes are cardinal features. Seminiferous tubule dysgenesis is a classic histologic feature of the testes. Individuals with Klinefelter syndrome exhibit a spectrum of gonadal failure, with many men going undiagnosed until they present with infertility in adulthood. However, a significant number come to attention during adolescence due to delayed puberty or lack of appropriate pubertal progression.

X chromosome abnormalities—Other X chromosome abnormalities, including Xq deletion and Triple X, can cause varying degrees of hypogonadism. Xq deletion can cause a phenotype similar to TS as well as isolated premature ovarian failure.[55] Deletions in the critical region, Xq13-q26, can also lead to premature ovarian failure.[56] Triple X, 47 XXX, is estimated to exist in 1 in 1000 girls and is marked by significant phenotypic variability.[57] Women with this condition can be tall and have normal external genitalia, with preservation of ovarian function.[57] These women can also have ovarian failure as well as significant genitourinary tract anomalies, including cloacal exstrophy and mullerian abnormalities.[58,59]

Abnormalities in gonadotropin production or action—Mutations within the β subunit of the gonadotropins, the gonadotropin receptors, or forms of resistance to gonadotropins can all result in hypergonadotropic hypogonadism. Females with mutations in the β subunit of FSH present with primary amenorrhea, delayed puberty, and poorly developed secondary sexual characteristics; they have low FSH levels, low estradiol levels, and high LH levels due to lack of feedback inhibition by estradiol.[60,61] Males with the same mutation have normal to delayed puberty and azospermia.[62]

A homozygous mutation within the LH β subunit has resulted in total functional loss in one male.[63] The individual in this case presented with delayed puberty, low serum testosterone, and high LH levels. It was discovered later that several male members in his family were infertile. In further studies, it was noted that females with this defect present with ovarian dysfunction, infertility, menstrual irregularity, or polycystic ovary syndrome.[64]

Inactivating mutations of the G-protein coupled FSH and LH receptors result in a phenotype similar to those with abnormalities in the LH and FSH β subunits. Complete LH resistance results from a loss of function mutation in the LH receptor gene. In males, this causes a phenotype that ranges from micropenis, to ambiguous genitalia, to completely female external genitalia.[65,66] In females, LH resistance results in normal puberty but subsequent amenorrhea, infertility, and elevated LH levels, demonstrating that ovulation requires LH as well as FSH.[67] FSH resistance due to FSH receptor mutations has also been reported,

particularly in the Finnish population. Women who are homozygous for this defect have gonadal dysgenesis and primary amenorrhea.[68] In contrast, men from the same kindreds have variable degrees of infertility.

A rare congenital condition associated with gonadotropin resistance is carbohydrate-deficient glycoprotein syndrome, which causes defects in gonadotropin glycosylation. In females with this defect, FSH seems to have less bioactivity and leads to decreased serum estradiol levels. However, exogenous FSH results in an increase in estradiol. Males with this disease advance through puberty but have decreased testicular volume.[69]

Resistance syndromes can also be due to variations in the signal transduction pathway after gonadotropin binding. Pseudohypoparathyroidism is a disease in which the signal transduction pathway of many hormones is altered due to inactivating mutations of the $G_s \alpha$ subunit. The mutation leads to multiple hormone resistance. In a study of 12 patients with pseudohypoparathyroidism, 25% of the pubertal patients had evidence of gonadotropin resistance.[70]

Disorders of sex development—Disorders of sex development (DSDs) are congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical.[71] This broad category includes common entities such as TS and Klinefelter Syndrome, as well as rare disorders such as cloacal exstrophy, mixed gonadal dysgenesis, and congenital aphallia. Many DSDs are associated with ambiguous genitalia, which is beyond the scope of this review. However, a few may present with delayed puberty or primary amenorrhea, and are important to consider in the differential diagnosis of an adolescent with apparent hypogonadism. These DSDs include Swyer syndrome, complete androgen insensitivity syndrome (CAIS), and rare forms of congenital adrenal hyperplasia (CAH), all of which result in female external genitalia.

Swyer syndrome: Swyer syndrome, also known as XY pure gonadal dysgenesis, is characterized by tall stature, primary amenorrhea, and delayed puberty in a phenotypic female. Laboratory studies reveal elevated gonadotropins, and ultrasonographic examination reveals bilateral streak gonads and a hypoplastic uterus.[72] Fifteen to thirty percent of these individuals have mutations in SRY (sex-determining region of the Y chromosome) or alterations in the Y chromosome.[73] There is also a high risk of gonadal tumors such as dysgerminoma or gonadoblastoma.[73] Therefore, gonadectomy is routinely recommended when this diagnosis is made.

Complete androgen insensitivity syndrome: CAIS is caused by mutations of the androgen receptor that result in loss of testosterone and dihydrotestosterone mediated action. Androgen receptor mutations are X-linked recessive in 70% of cases, and are found in 1 in 20,000 to 1 in 90,000 genetic males.[74] The most common phenotype is that of an adolescent girl who has normal breast development, but absent or scant body hair and primary amenorrhea. Examination of the external genitalia reveals a normal female phenotype with a blind ending vagina. Eighty percent to 90% of girls with CAIS will also eventually develop inguinal hernias,[75] with some presenting in infancy with this diagnosis.

Congenital adrenal hyperplasia: Rare forms of CAH can present with hypogonadism due to lack of production of testosterone and estrogen. These conditions include deficiencies of 17α-hydroxylase, side chain cleavage enzyme (SCC), and steroid acute regulatory protein (StAR). Girls with 17α-hydroxylase deficiency can present with primary amenorrhea and absent secondary sexual characteristics. Boys have female external genitalia, a blind vagina, and intra-abdominal testes.[76] Hypertension and hypokalemia may also be present.[77] SCC is the first step in the steroidogenic pathway and converts cholesterol to pregnenolone. SCC deficiency leads to deficiencies in all steroid hormones. SCC deficiency in genetic males leads to XY sex reversal and adrenal insufficiency.[78] StAR, a protein expressed in the adrenal cortex and gonads, increases cholesterol transport in response to steroidogenic stimuli. Affected genetic males present in early infancy with adrenal crisis, and appear phenotypically female.[79] Affected genetic females are normally developed at birth and may have intact ovarian function.[80]

Galactosemia: Another congenital cause of primary hypogonadism is galactosemia. Galactosemia results from a deficiency in galactose-1-phosphate uridyltransferase (GALT) and presents with clinical manifestations of cataracts, *Escherichia coli* sepsis, poor growth, and feeding dysfunction if undiagnosed in the newborn. In an initial study conducted in 1981, gonadal function was evaluated in 12 women and 8 men with galactosemia. Although gonadal function was normal in men with the disease, the women in this study had evidence of hypergonadotropic hypogonadism, with varying degrees of primary and secondary amenorrhea and oligomenorrhea.[81] Ultrasound studies of the ovaries in those affected demonstrated streak gonads in several women.[81] The cause of the hypogonadism is most likely premature ovarian failure, although the exact pathophysiology is not well understood. Numerous theories exist, including the hypothesis that galactose-1-phosphate is toxic and perhaps competitively inhibits UDP-Galactose transferase and alters FSH and FSH receptors, with subsequent failure of ovarian follicles to develop.[82] This process manifests as an elevated FSH in 85% of girls younger than 10 years who have galactosemia and premature ovarian failure.[82]

Testicular regression sequence: Testicular regression sequence (TRS), or vanishing testis syndrome, occurs when an initially normal testicle that existed in fetal life subsequently atrophies. Most individuals with TRS have normal male external genitalia, reflecting that normal testicular function existed during prenatal life. The most likely cause of this syndrome is fetal or antenatal testicular torsion, or trauma to scrotal contents in utero.[83] This view is supported by the finding of hemosiderin laden macrophages and dystrophic calcifications under histopatholgic examination.[84] There has also been an association noted between testicular regression and persistence of mullerian duct structures.[85] Thus far, a search for a molecular genetic cause of TRS has been negative.[86]

Acquired Origins

The acquired forms of primary hypogonadism are as varied as the congenital forms. Important acquired origins include treatment for pediatric cancer (radiation and chemotherapy) and autoimmune conditions.

Chemotherapy and radiation—Both chemotherapy and radiation have been noted to cause primary hypogonadism. In girls, the dose of intra-abdominal radiation needed to destroy more than 50% of developing oocytes is less than 2 Gy.[87] In the 70% of patients who survive pediatric cancer, 1 in 6 female survivors develops primary ovarian failure. Those who do undergo spontaneous menarche have decreased ovarian reserve.[88] In boys, depressed spermatogenesis can be seen after a testicular radiation dose as low as 0.15 Gy, with temporary azoospermia occurring after doses of 0.3 Gy.[89] The effect of radiation on testicular function is age dependent, with prepubertal radiation exposure causing significantly more damage to Leydig cells than postpubertal radiation.[90] Cumulative doses of alkylating agents are also correlated with altered function.[89]

A high prevalence of hypogonadism was noted in young adult survivors of childhood cancer who participated in a study comparing 3 treatment arms for non-Hodgkin lymphoma (NHL) and acute lymphoblastic leukemia (ALL). The study compared treatment with chemotherapy alone (vincristine, prednisolone, l-asparaginase, methotrexate, 6-mercaptopurine), combined chemotherapy and prophylactic cranial radiation, and chemotherapy with total body radiation and bone marrow transplant. All women in the third category had premature ovarian failure. Women in the other 2 categories, however, had intact ovarian function. Among men in the third category, 83% had primary hypogonadism, with a low serum testosterone and elevated FSH and LH. Forty percent of men in all 3 treatment arms had alterations in spermatogenesis, with the greatest dysfunction appearing in those who had received total body radiation.[91]

Despite these findings, there have been reports of spontaneous recovery of testicular or ovarian function in childhood cancer survivors. Although more common in older children and adults, recovery of ovarian function has occurred as long as 12 years post exposure to radiation and alkylating chemotherapy in a young girl.[92] Due to the increased risk of gonadal dysfunction in pediatric cancer patients and also due to the chance of spontaneous recovery, recommendations for surveillance include yearly monitoring of pubertal status with Tanner staging and assessment of growth velocity. Laboratory measurements of FSH and LH as well as estradiol or testosterone are recommended for those with signs of pubertal delay.[93]

Autoimmune gonadal failure—Autoimmunity can lead to both testicular and ovarian failure, specifically in those who have other types of autoimmune endocrinopathies. Several autoimmune polyglandular syndromes (APS) have been identified. Of these, APS I and APS II have been associated with premature ovarian failure at prevalence rates of 30% to 50%.[94] APS I consists of a triad of hypoparathyroidism, mucocutaneous candidiasis, and adrenal insufficiency. The mutation is within the *AIRE* gene, the autoimmune regulator. In a Finnish cohort, approximately 50% of the females identified with APS I had premature ovarian failure. Two-thirds of these individuals had autoantibodies to side-chain cleavage enzyme (anti-SCC),[95] one of the enzymes identified in steroid production that is specific to the ovary and is noted in autoimmune ovarian failure. In those who have been diagnosed with APS I and who initially have signs of ovarian failure, the presence of steroid cell antibodies may signal progression of the disease process.[96] APS II consists of autoimmune adrenocortical failure along with thyroid disease or diabetes. Positive antibodies to the P450 enzymes,

specifically ovary-specific antibodies, in the steroid production pathway are thought to mediate autoimmune ovarian failure in this syndrome as well.[97] Autoimmunity can also cause isolated premature ovarian failure,[98] and has also been reported in conditions such as systemic lupus erythematous and myasthenia gravis.

Testicular failure occurs at a lower rate than ovarian failure in APS.[99] Autoimmunity to the Leydig cells in APS may be mediated by P450 autoantibodies that are testis specific.[100] Antisperm antibodies have also been noted in prepubertal boys treated with chemotherapy and in those with urogenital tract abnormalities such as cryptorchidism, testicular torsion, or hypospadias.[101]

EVALUATION

Evaluation of a child with delayed puberty begins with a careful history and physical examination. Important elements on history include the parents' pubertal timing, because late menarche in the mother or delayed completion of adult height in the father is strongly suggestive of CDGP. Eliciting a family history of hypogonadism, autoimmune syndromes, DSDs, or consanguinity is also essential. History in the child should include attention to any CNS insult or symptoms of chronic disease. In the review of systems, lack of sense of smell can be an important clue to the presence of KS.

Physical examination should include height and weight measurements. Neurologic assessment should include evaluation of visual fields. Assessment of secondary sexual characteristics includes Tanner staging and recognition of evidence of androgen exposure. Testicular enlargement, which can sometimes go unnoticed by boys, indicates the onset of central puberty. Stigmata of TS or Klinefelter Syndrome should be noted. The external genitalia should be visually inspected for any signs of anatomic abnormality.

Laboratory evaluation including plasma gonadotropin levels, estradiol, or testosterone may be helpful. Low gonadotropin levels suggest CDGP or pathologic hypogonadotropic hypogonadism, and can be further evaluated with a GnRH stimulation test.[102] In contrast, elevated gonadotropins indicate primary gonadal failure. A bone age radiograph is an essential component of the evaluation. Other tests that may be indicated, depending on the individual situation, include a head MRI, karyotype, auto-immune panel, or molecular genetic analysis. In patients with suspected CDGP, a "wait and see" approach is typically employed to determine whether spontaneous puberty will ensue.

TREATMENT

Although there are many causes of hypogonadism in children, the treatment is primarily focused on hormone replacement with sex steroids. The overarching goal is to simulate a normal progression of pubertal development that also allows for the attainment of genetic potential for height.

Estrogen Replacement

Estrogen therapy is initially started for pubertal induction and breast development in girls with hypogonadism. Studies regarding estrogen therapy in children have focused primarily

on girls with TS. Recommended starting doses of estrogen therapy in this population are one-eighth to one-tenth the doses used for adult replacement, and vary depending on the formulation used. Very low doses have been reported to have a salutary effect on linear growth in TS.[103] Multiple different formulations of estrogen are available, and include oral estradiol, oral conjugated estrogen, trans-dermal estrogen patches, and estrogen gel. The age at which estrogen therapy is initiated is individualized and incorporates factors such as chronologic age, bone age, absolute height, and psychosocial issues. The starting dose is low and is gradually increased over several years. Equivalent adult doses of oral therapy are micronized estradiol, 2 mg, esterified estrogen, 1.25 mg, ethinyl estradiol, 8 to 10 μg, and conjugated estrogens, 1.25 mg.[104] Addition of progesterone 1 week per month, usually in the form of medroxyprogesterone, after 1 to 2 years of estrogen therapy or post breakthrough bleeding, allows for adequate breast and uterine development. Formulations and available does of estrogen preparations are shown in Table 3.

Limitations of oral estrogen therapy include variable bioavailability due to first-pass metabolism within the liver, which subsequently affects liver function and clotting factors.[105,106] As a result, transdermal estrogen formulations are gaining in popularity. Estrogen patches are widely used in adult women, and doses of 0.625 and 1.25 mg of oral conjugated estrogens have been reported to be similar those of 50 and 100 μg of transdermal estradiol per 24 hours.[107] Pubertal induction can be accomplished with transdermal estradiol at a dose as low as 3.1 to 6.2 μg/24 hours.[106] Puberty can then be mimicked with subsequent doubling of the dose after a median duration of 8 months and addition of progesterone 2 years after estrogen initiation. A transdermal estrogen dose of 0.1 mg/d is equivalent to an adult regimen. When comparing transdermal estrogen to oral estrogen, significantly higher levels of 17β-estradiol were noted with oral estrogen. However, no differences in metabolic effects including lipolysis, lipid, and carbohydrate oxidation, and resting energy expenditure from short-term transdermal versus oral estrogen therapy have been noted.[105] In contrast, a pilot study of transdermal versus oral conjugated estrogen in girls with TS found better bone mineral accrual and uterine development in the transdermal group.[108] Percutaneous estradiol gel has also been investigated for pubertal induction in girls with TS at a starting dose of 0.1 mg nightly with increases of 0.1 mg for each additional year up to 5 years. Side effects of percutaneous gel therapy include local skin irritation, and this modality is not currently in use in the clinical setting.[109] For hypogonadal women, estrogen replacement is needed throughout reproductive life.

Testosterone Replacement

In boys, studies involving testosterone for pubertal induction have primarily focused on CDGP and KS. Testosterone therapy is usually initiated at 15% to 25% of adult doses. Approximately 50 to 100 mg of a testosterone ester formulation is given intra-muscularly every 2 to 4 weeks for 4 to 6 months with gradual increases to adult doses.[110,111] In boys with CDGP, a 4- to 6-month course of 50 to 100 mg testosterone per month may be offered to bring about initial secondary sexual characteristics and boost linear growth.[110] In boys who have permanent hypogonadism, the need for therapy is lifelong. Even at the initial doses used for pubertal induction, there is a decrease in total fat mass, percent body fat, and whole body proteolysis once testosterone is initiated.[112]

Intramuscular, transdermal, and oral formulations of testosterone exist. The preparations testosterone enanthate and testosterone cypionate are the most often used formulations in children, due to the difficulty in delivering the small doses needed initially for pubertal induction with alternate forms.[113] Intramuscular injections of testosterone, however, can be painful for the adolescent patient population, and studies investigating other formulations are ongoing.

Formal guidelines regarding the use of oral preparations have yet to be delineated, and experience with this form of testosterone is far less than with the intramuscular form. Transdermal testosterone, in the form of testosterone gel, at doses of 50 mg/m^2/d has been used in children short-term to treat poor growth secondary to renal failure.[114] In a study of transdermal testosterone delivered via a 5-mg patch, overnight use in boys with delayed puberty resulted in pubertal testosterone concentrations as well short-term growth.[115] Side effects of transdermal testosterone include local skin irritation. As in oral testosterone therapy, there are limited studies regarding the use of transdermal preparations of testosterone, and intramuscular testosterone therapy remains the mainstay of therapy for pediatric patients. Testosterone preparations and adult doses are shown in Table 4.

Adjunctive treatment in the form of human chorionic gonadotropin has been suggested in boys with PWS in whom beneficial effects on body composition and endogenous testosterone secretion have been observed.[116]

SUMMARY

In conclusion, causes of hypogonadism are heterogeneous and may involve any level of the reproductive system. Whereas some conditions are clearly delineated, the exact etiology and underlying pathogenesis of many disorders is unknown. Regardless of the form of hypogonadism, the crux of therapy in children revolves around sex steroid replacement. Continued molecular genetic investigation and prospective clinical trials will enhance knowledge and improve management of hypogonadism in pediatric patients.

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Table 1

Molecular genetic causes of hypogonadotropic hypogonadism

Gene	Product	Inheritance	Target Sites	Additional Clinical Manifestations
SF-1	Orphan nuclear receptor	Autosomal recessive	Steroidogenesis in males Hypothalamus Pituitary Adrenals	XY sex reversal, adrenal failure In females: adrenal failure, normal ovarian function
DAX-1	Orphan nuclear receptor	X-linked recessive	Steroidogenesis Hypothalamus Pituitary Adrenals	In males: spectrum of hypogonadotropic hypogonadism and adrenal insufficiency
KAL-1	Anosmin	X-linked recessive	Hypothalamic neuronal migration	Anosmia
FGFR1	FGF receptor	Autosomal dominant	FGF receptor in hypothalamus Pituitary	Cleft palate Agenesis of corpus callosum
GPR54	G protein coupled receptor	Autosomal recessive	GnRH-secreting neurons Pituitary	Isolated hypogonadotropic hypogonadism
Prop-1	Transcription factor	Sporadic autosomal recessive	Pituitary gonadotrope development	Growth hormone deficiency Central hypothyroidism
Hesx1	Transcription factor	Sporadic	Prop-1 Pituitary gonadotrope development	Septo-optic dysplasia Central hypothyroidism Central hypocortisolism Diabetes insipidus
LEP	Leptin	Autosomal dominant	Hypothalamus	Obesity Hyperphagia T-cell immune dysfunction
LEPR	Leptin receptor	Autosomal dominant	Hypothalamus	Obesity Hyperphagia T-cell immune dysfunction

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Table 2

Causes and clinical manifestations of congenital hypergonadotropic hypogonadism

Abnormality	Clinical Manifestations	
Turner syndrome	Short stature, webbed neck, cubitus valgus	
	Streak ovaries	
Klinefelter syndrome	Tall stature	
	Eunuchoid body habitus	
	Small, firm testes	
X chromosome abnormality	Xq-premature ovarian failure	
	XXX-tall stature	
	GU abnormalities	
FSH and LH β subunit mutations	*Males*	*Females*
	Delayed puberty	Primary amenorrhea
	Azospermia	Menstrual irregularity
	Infertility	Polycystic ovary syndrome
FSH and LH receptor mutations	*Males*	*Females*
	Micropenis	Primary amenorrhea
	Ambiguous genitalia	Gonadal dysgenesis
	XY sex reversal	
	Infertility	
Swyer syndrome (46, XY)	Tall stature	
	Primary amenorrhea	
	Delayed puberty	
	Gonadal tumors	
CAIS (46, XY)	Primary amenorrhea	
	Normal breast development	
	Sparse body hair	
	Absent mullerian and wolffian structures	
CAH (depending on deficiency)	Hypertension	
	Hypokalemia	
	XY sex reversal	
	Adrenal crisis	
Galactosemia	Ovarian failure	
Testicular regression sequence	Normal external genitalia	

Table 3

Estrogen formulations

Type of Estrogen	Trade Name	Available Doses
Oral estradiol	Estrace	0.5, 1, 2 mg
	Gynodiol	0.5, 1, 2 mg
Oral esterified estrogen	Menest	0.3, 0.625, 1.25, 2.5 mg
	Ogen	Equivalent to 0.625 mg and above
	Ortho-Est	Equivalent to 0.625 mg and above
Oral conjugated equine estrogen	Premarin	0.3, 0.45, 0.625, 0.9, 1.25 mg
Estradiol patches	Vivelle	0.025, 0.0375, 0.05, 0.075, 0.1 mg/d
	Menostar	0.014 mg/d
Estradiol gel	Divigel	0.5 mg estradiol/5 g gel

Table 4

Testosterone formulations

Formulation	Trade Name	Dose (Adult)
IM testosterone enanthate	Delatestryl	250 mg every 2–4 wk
IM testosterone cypionate	Depo-Testosterone	250 mg every 2–4 wk
Oral testosterone undecanoate	Andriol (40 mg capsules)	2 capsules (2–3 times per day)
Testosterone patch	Androderm	5 mg/patch changed twice weekly
Testosterone gel	Androgel (25 mg testosterone/2.5 g gel) (50 mg testosterone/5 g gel)	50–100 mg/d
Buccal testosterone	Striant 30 mg tablet	1 tablet twice a day
Testosterone implants	Testopel 75 mg per pellet	3–4 pellets every 4–6 mo