Hormones (2018) 17:439–449
https://doi.org/10.1007/s42000-018-0067-8

REVIEW

Pediatric endocrinology: an overview of the last decade

Lourdes Ibáñez[1,2] · Konstantina Barouti[3] · Georgios K. Markantes[3] · Anastasia K. Armeni[1,3] · Neoklis A. Georgopoulos[1,3]

Received: 7 June 2018 / Accepted: 30 August 2018 / Published online: 6 October 2018

Abstract
Over the past decade, considerable progress has been made in the field of pediatric endocrinology. However, there is still a long way to go regarding the exploration of novel avenues, such as epigenetics, the changing views on the pathophysiology and derived therapy of specific disorders, and the prevention of prevalent diseases. The next decade will hopefully bring the consolidation of most of those achievements and the development of new pathways for further progress.

Keywords Pediatric endocrinology

The past decade has brought a substantial number of consensus papers related to pediatric disorders or focused on the pediatric care of disorders lasting into adulthood. While some of these consensus papers have changed entire paradigms, others have not been endorsed as anticipated. They have all nevertheless been incorporated into clinical practice despite their limitations (and sometimes possibly because of them). Over the last 10 years, the long-term outcome of some therapies (e.g., growth hormone) has been tested further, allowing the attainment of solid conclusions regarding both beneficial and adverse effects; it has also been possible to guide new therapeutic approaches departing from changing views on the pathophysiology of specific disorders (e.g., ovarian androgen excess or polycystic ovary syndrome—PCOS). Prevention has been proposed as a useful approach to address some conditions, such as overweight and obesity, which, in turn, have been shown to influence physiological processes, such as adrenarche and pubertal timing, with potential effects on final height and adult health. Prenatal pharmacological intervention in individuals at risk for genetic diseases—for instance, congenital adrenal hyperplasia (CAH)—in order to avoid subsequent disease-related complications remains controversial. Finally, genetic and epigenetic studies have expanded our knowledge in relation not only to the pathology but also to the physiology of many endocrine disorders, for example, the relationship between body fat acquisition and pubertal timing.

This work was presented at the Endorama Meeting, held in Patras 26–27th January 2017

✉ Lourdes Ibáñez
libanez@hsjdbcn.org

[1] Pediatric Research Institute Sant Joan de Deu, University of Barcelona, Esplugues, Barcelona, Spain & CIBERDEM, Instituto de Salud Carlos III, Madrid, Spain

[2] Hospital Sant Joan de Déu, University of Barcelona, 08950 Esplugues, Barcelona, Spain

[3] Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University of Patras Medical School, Patras, Greece

Birthweight and post-natal weight gain: association with adrenarche and pubertal onset and progression

Over the last decade, obesity has developed into a worldwide epidemic, with, notably, the rapidly rising percentage of overweight and obese children and adolescents in Western countries being particularly alarming. Though obesity, which is accompanied by adverse effects in a large number of organs/systems, has always existed, it is today considered a modern disease because of its very wide prevalence.

Besides other well-known comorbidities associated with obesity, excess weight has been shown to influence physiological processes, such as adrenarche and puberty. Birth weight is also an important factor affecting these processes. Non-obese girls with precocious pubarche (PA) (i.e., appearance of pubic hair before the age of 8 years), born appropriate for gestational age (AGA), have normal pubertal timing but may have early menarche [1]. Thus, although precocious pubarche in AGA girls can be viewed as a benign condition,

the occurrence of early menarche may accelerate epiphyseal closure and reduce final height. A meta-analysis involving almost 2,400 subjects concluded that girls born small for gestational age (SGA) may have earlier onset of puberty as well as earlier menarche as compared with AGA controls girls. In boys, however, there was no difference in the timing of puberty [2]. Uçar et al. demonstrated that among prepubertal girls with precocious adrenarche (PA), those born SGA presented reduced insulin sensitivity and IGF-binding-protein-1 concentrations and a higher prevalence of multicystic ovaries as compared with PA girls born AGA.

A mismatch between lower prenatal weight and higher postnatal weight gain has been shown to influence the timing and intensity of adrenarche and puberty as well as the rate of pubertal progression, particularly in girls. This mismatch may also be a risk factor for the subsequent development of androgen excess or PCOS in adolescence, even in the absence of obesity [3]. In girls with low birthweight and post-natal catch-up, PA/pubarche may be a forerunner of the metabolic syndrome and be followed by advanced puberty with early menarche, reduced final height, and ovarian androgen excess (PCOS) in adolescence. Accumulation of excess visceral fat (including hepatic fat), together with hyperinsulinemia and most likely modulated by epigenetic factors, underlies the development of this sequence [4].

In rapidly maturing girls with low birthweight, precocious pubarche, and central adiposity, early metformin therapy (age 8–12 years) normalizes bone maturation (as assessed by an automated method), delays menarche toward normal, augments adult height (by approximately 4 cm), and reduces total, visceral, and hepatic adiposity. The normalization of bone maturation is related to the reduction of central fat and more specifically to hepatic fat, suggesting that central adiposity—in particular, hepatic adiposity—is an endogenous accelerator of maturation in girls [5]. Early metformin treatment also has the potential to prevent or delay the development of hirsutism, androgen excess, oligomenorrhea, and full-blown PCOS in adolescence, indicating that late childhood and early puberty are more critical windows for PCOS prevention than the first years beyond menarche [6].

Novel insights into the etiology, treatment, and outcome of central precocious puberty

Etiology

Central precocious puberty (CPP) results from the premature reactivation of the hypothalamic-pituitary-gonadal axis; the etiology of most cases of so-called "idiopathic CPP" remains elusive. An initial study performing whole-exome sequencing in patients with familial CPP in 2013 identified four novel heterozygous mutations in MKRN3, the gene encoding makorin RING-finger protein 3; both sexes were equally affected. MKRN3 is a paternally expressed, imprinted gene located in the Prader-Willi syndrome critical region (chromosome 15q11–q13). The mutations initially described included three frameshift mutations predicted to encode truncated proteins, and one missense mutation thought to disrupt protein function [7]. Additional mutations in MKRN3 have been described in sporadic cases of CPP, albeit their frequency is lower than in familial CPP. Genetic analysis of MKRN3 should nowadays be included in the routine clinical investigation of familial and idiopathic CPP.

After this pioneer study, several investigators aimed to clarify the role of this protein in the timing of pubertal onset. Longitudinal studies in healthy Danish girls and boys have unveiled a decline in serum MKRN3 concentrations in the years preceding pubertal onset. The decrease in serum MKRN3 levels is maintained throughout puberty and is inversely correlated with serum gonadotropin concentrations, supporting the notion that MKRN3 is a major inhibitor of hypothalamic GnRH secretion during childhood. Interestingly, girls with CPP show undetectable or very low levels of this protein [8,9].

Treatment

Depot formulations of GnRH analogues (GnRHa) have so far been the cornerstone of CPP treatment, effectively suppressing gonadotropin secretion and thus modulating bone maturation and preserving height potential. The 50-mg histrelin implant has emerged as an alternative therapeutic option. The implant—which is inserted subcutaneously—provides continuous release of the GnRHa histrelin and adequately suppresses the hypothalamic-pituitary-gonadal axis within 1 month, resulting in pubertal arrest, attenuation of skeletal advancement, and an increase in predicted adult height. The implant is marketed for annual use, but suppression may last up to 2 years. Placement and removal of the device are easily performed by an experienced pediatric surgeon. The major downside is a ~ 25% rate of breakage upon removal. The average time to menarche following explantation is comparable to that of depot GnRHa formulations, albeit with wide interindividual variation [10].

Outcome

While the use of GnRHa to suppress gonadotropin secretion and prevent the adverse effects of CPP on physical appearance, bone maturation, and final height has been proven to be safe and effective, data on the long-term health outcomes of treated and untreated CPP subjects are sparse. Some studies show an association of CPP with increased adult BMI, cardiovascular risk factors, breast and reproductive tract cancers. Two recent studies from Israel have followed treated and untreated women with CPP for several years and reported increased rates of clinical androgen excess in adulthood (irrespective of treatment), compared to controls. Pharmacologic pubertal suppression may have a protective effect, as fertility

problems were more prevalent only among untreated patients [11]. With respect to non-reproductive sequelae, the authors disclosed that CPP (treated or untreated) is not associated with increased risk of obesity, metabolic derangements, or cancer morbidities in young adulthood [12].

Genetics of delayed puberty

Late pubertal onset is a relatively common disorder, affecting around 3% of adolescents. Although this delay in the appearance of secondary sexual characteristics might be extremely disturbing for the patient and/or the family, the vast majority of cases are self-limited and not associated with underlying disease.

Self-limited delayed puberty is a common condition that segregates within families, mostly following the autosomal dominant pattern. However, the causal genetic factor is as yet unknown. Howard et al. showed that mutations in the immunoglobulin superfamily member 10 gene (IGSF10) might lead to delayed puberty, presumably by reducing migration of GnRH neurons [13].

The same authors have subsequently identified, by means of whole exome sequencing, the contribution of rare variants in genes that are important to pubertal timing and body mass regulation in the general population, to the phenotype of familial delayed puberty. These findings may partially explain the extremes of variability in cases of "constitutional" delayed puberty [14].

Polycystic ovary syndrome

PCOS is a complex heterogeneous disorder. Though long known to medical science, it is still today a mystery, with the pathophysiology, diagnostic criteria, and therapeutic approach to adolescent PCOS remaining particularly elusive. For this reason, a collaborative effort initiated by a number of pediatric endocrine societies has resulted in a first global update on the disorder. The document offers a developmental perspective of PCOS and documents the main directions followed by past and present investigations into adolescent PCOS and which are likely to be the directions of future research. The main conclusions are set out below.

- The pathophysiology of PCOS is most probably multifactorial and involves the interaction of genetic and epigenetic changes, primary ovarian abnormalities, neuroendocrine alterations, and endocrine and metabolic modifiers, such as anti-Müllerian hormone, hyperinsulinemia, insulin resistance, adiponectin, and adiposity [15].
- The diagnosis of PCOS in adolescence can be problematic, primarily because the diagnostic pathological features used in adult women may be normal pubertal physiological events. Appropriate diagnosis of adolescent PCOS should include evaluation of symptoms related to increased androgen action, such as hirsutism or severe acne, as well as menstrual irregularities 2 years beyond menarche. Establishing biochemical hyperandrogenemia (testosterone and/or free testosterone) is also necessary. Polycystic ovarian morphology, hyperinsulinemia, insulin resistance, and obesity may be present in adolescents with PCOS, but are not considered to be diagnostic criteria [15].
- Treatment of adolescent PCOS should include lifestyle intervention, local therapies, and oral medication. Insulin sensitizers like metformin and oral contraceptive pills provide short-term benefits for PCOS symptoms. There are limited, albeit convincing, data on combined therapies of antiandrogens and insulin sensitizers resulting from new pathophysiological insights showing additive/synergistic actions [15].

Obesity is considered a cardinal feature of PCOS, existing in up to two-thirds of adult patients. Obese individuals are at a higher risk for comorbidities, such as the metabolic syndrome and cardiovascular disease. The combination of obesity and PCOS further increases this risk, as obesity exacerbates the reproductive and metabolic manifestations of the syndrome. Furthermore, obesity starting in prepuberty is a risk factor for PCOS development during adolescence [16]. Therefore, weight loss should be a primary treatment target in obese individuals with PCOS. In fact, Lass et al. demonstrated that weight loss via lifestyle intervention was very effective in normalizing menses, reducing androgen levels, and attenuating cardiovascular risk factors in obese PCOS adolescents [17].

PCOS is thought to originate most often from an absolute or relative excess of fat in subcutaneous adipose tissue and from an ensuing excess of hepatic and visceral fat with elevations of insulin and gonadotropin secretion. In adolescent girls with PCOS and without pregnancy risk, treatment with a low-dose combination of spironolactone, pioglitazone, and metformin was accompanied by a reduction of hepato-visceral fat (without loss of weight) and was followed by a more normal ovulation rate than standard treatment with an oral contraceptive: it may thus partially prevent the risk of oligoanovulatory subfertility. More on-treatment loss of central fat excess was followed by more post-treatment ovulations. The sequential findings in the present study corroborate a concept wherein hepato-visceral fat and/or hyperinsulinemia are key PCOS drivers [18].

Insulin resistance

Insulin resistance is a common condition among children and adolescents: it is related to cardiometabolic risk and its early

detection has become a challenge. The rate of childhood growth in height and weight appears to influence the development of insulin resistance. A consensus meeting in 2010 underlined the lack of a clear cutoff to define insulin resistance in children and showed that surrogate measures, such as fasting insulin, are poor estimates of insulin sensitivity. No evidence for screening children, even when obese, for insulin resistance has been agreed upon. Prevention strategies including lifestyle changes should be implemented early in life, while metformin should only be used in selected cases [19].

Multiple studies have shown that either low or high birthweight, or adverse early life exposures, increase the risk of type 2 diabetes in later life [20]. A prospective cohort study of 4,328 children looked for associations between length and weight from fetal life onwards with insulin and C peptide levels [21]. The results suggested that weight increase in each time interval from birth onwards, length growth from 6 months onwards, and BMI increase from 12 months onwards were positively associated with insulin levels during childhood. The strongest associations were present for weight and BMI growth between age 48 and 72 months. Moreover, prenatal growth was not associated with childhood insulin or C- peptide levels, independent of growth in other time intervals.

Obesity

One in four children in the USA aged from 2 to 19 years is overweight or obese [22]. Obesity is associated with reduced life expectancy due to comorbidities like insulin resistance, dyslipidemia, and hypertension, which are cardiovascular risk factors. Although the overall rate of pediatric obesity has stabilized over the last decade after a steady increase for three decades, obesity rates continue to rise in certain populations. The US Preventative Services Task Force recommends screening for obesity in children 6 years and older and referring these patients for intensive behavioral interventions in order to improve their weight status. Less intensive interventions, as well as medications such as metformin and orlistat, are of uncertain clinical significance and therefore are not recommended [23].

Although lifestyle intervention is the treatment of choice for overweight children, the amount of obesity reduction required to achieve improvements in cardiovascular risk factors was not clearly defined until 2016. Reinehr et al. assessed the association between BMI reduction and CVD improvement and found that a reduction of 0.25 during a period of a year is sufficient to improve hypertension, hypertriglyceridemia, and HDL cholesterol, but had no effect on LDL cholesterol or glucose levels. A reduction of 0.5 or greater doubles the effect [24].

The complications of childhood obesity clearly highlight the urgent need for effective preventive strategies. An association between early life indicators and later life obesity risk would be very helpful in the development of these strategies. Evidence from numerous studies supports the notion that rapid post-natal weight gain is a risk factor for later life obesity [25,26]. A meta-analysis of a birth cohort from three European countries demonstrated positive associations between genetic obesity susceptibility and post-natal gains in weight and length during infancy. In addition, positive associations with both fat and lean mass in infancy and early childhood have been noted. Symmetrical rapid growth may identify infants at risk for childhood and adult life obesity [27].

Growth restraint before birth confers more risks for obesity and insulin resistance, particularly when followed by excessive weight gain after birth. Placenta and cord blood from children born SGA presented differential methylation and expression patterns involved in the regulation of glucose homeostasis and lipid metabolism. These epigenetic factors may influence fetal growth, early body composition, and diabetes risk throughout the patient's lifetime [28].

Diabetes

Type 1 and type 2 diabetes are nowadays highly prevalent disorders among children and adolescents, with prevalence having increased significantly for both types from 2001 to 2009 in most age, sex, and race groups [29]. The incidence of type 1 diabetes, which is the most common type in youth, has risen significantly over the past 3 decades. Several studies have reported an increasing percentage of young people with apparent type 2 diabetes, a disease that has traditionally been viewed as a disorder of adults; high rates of type 2 diabetes are evident mostly among adolescents aged 15–19 years [30,31].

These recent epidemiologic trends in both type 1 and type 2 diabetes raise the question of whether the pattern of complications differs depending on the diabetes type at similar ages and on diabetes duration. An observational study of 1,746 patients suggested that the prevalence of diabetic kidney disease, diabetic retinopathy, peripheral neuropathy, arterial stiffness, and hypertension was higher among subjects with type 2 diabetes as compared to those with type 1, whereas cardiovascular autonomic neuropathy was not notably different between the two groups [32]. These findings support the implementation of early close monitoring of children with diabetes in order to avoid comorbidities.

Although complications such as atherosclerosis and cardiovascular disease are rare among children with type 1 diabetes, early intervention can potentially further decrease mortality. Chrysis et al. assessed simultaneously in young patients with type 1 diabetes the serum concentrations of four proteins (osteoprotegerin—OPG, asymmetricdimethylarginine—ADTA, fetuin A, and RANKL) involved in vascular health and considered to be biomarkers for the assessment of cardiovascular risk in adults. OPG was found to be increased and ADMA was

decreased, but fetuin A and RANKL were stable. As increased OPG has been associated with cardiovascular risk, it may be clinically useful in the assessment of cardiovascular risk in diabetic children [33].

Intrauterine exposures to maternal diabetes and obesity have been reported to be strongly associated with type 2 diabetes in youth. The association between diabetes type 2 in later life and exposure to diabetes type 2 in utero may be explained by genetic susceptibility, intrauterine effects, and epigenetic factors. Furthermore, maternal obesity can lead to childhood overweight, which may increase the risk for type 2 diabetes due to genetic predisposition paired with excess calorie availability post-natally. In multiethnic populations, up to 47% of type 2 diabetes in youth could be attributed to the combined effect of these exposures [34].

Congenital hyperinsulinism

Congenital hyperinsulinism (HI) is a relatively rare disease characterized by hyperinsulinemic hypoglycemia caused by excess secretion and dysregulation of insulin. It is the most frequent cause of severe, persistent hypoglycemia in newborns and infants. Prompt treatment of hypoglycemia is essential to prevent brain damage. Recommended first-line pharmacological treatment consists of diazoxide combined with chlorothiazide. Octreotide, a short-acting somatostatin analogue, inhibits the release of insulin and is frequently used as second line therapy. A study of 27 patients from six different European centers who received long-acting somatostatin analogues demonstrated the efficacy of this medication as an alternative therapy [35]. The only notable side effect was an elevation of liver enzymes. The recommendation thus is for careful monthly monitoring of hepatic enzymes in patients treated with long-acting somatostatin analogues. Another study performed in four patients, unresponsive to diazoxide and octreotide, who received the mTor inhibitor sirolimus, reported that all patients were responsive to therapy, although one of them received additional doses of octreotide to maintain stable glucose levels. No significant side effects were observed. Hence, mTor inhibitors may be a plausible option for patients who would otherwise require pancreatectomy [36].

Thyroid disorders

Hypothyroidism

Congenital hypothyroidism (CH) is a condition of inadequate thyroid hormone production in newborn infants occurring in approximately 1:2000 to 1:4000 newborns and is one of the most common causes of intellectual disability [37]. Considering the fact that the majority of cases are sporadic and that most newborns with CH have few or no clinical manifestations of thyroid hormone deficiency, it is impossible to identify in advance which infants are likely to be affected. Accordingly, screening programs have been developed to detect the condition as soon as possible.

Given the importance of optimal screening and early diagnosis, the European Society for Pediatric Endocrinology (ESPE) examined the current best practice in CH and derived evidence-based recommendations. The need to identify clear cutoff thresholds for CH screening without increasing the number of false positive results is highlighted. Worldwide neonatal screening is strongly recommended as well as second screening in special high-risk categories, immediate LT4 supplementation when there is an elevated suspicion for CH, periodic treatment monitoring, and regular evaluation of growth, metabolic, and cardiovascular health as well as psychomotor development [38].

However, according to Mengreli et al., several CH cases can be missed when a TSH threshold of 20 Mu/L is applied. When a TSH cutoff point of 10 Mu/L was used, a significant percentage of new cases was diagnosed. These undiagnosed cases were mostly premature infants. Nevertheless, the increase in false positive cases when reducing the TSH threshold remains a severe disadvantage which should be balanced against the complications of thyroid dysfunction at this important development stage [39].

Subclinical hypothyroidism (SH) is a condition characterized by normal circulating levels of thyroid hormones with mildly elevated TSH serum concentrations in asymptomatic patients. A multicenter study by Wasniewska et al. evaluated the evolution of idiopathic SH in children and adolescents. Two-year follow-up of these patients showed a normalization or maintenance of TSH values over time. Furthermore, TSH changes were independent of free thyroid hormone levels and clinical status. Therefore, juvenile SH can be considered as a benign condition with a very low risk of evolution toward overt hypothyroidism [40].

Thyroid hormones function through alpha 1, beta 1, and beta 2 nuclear receptors, namely, the thyroid receptors. TRA1 subtype is expressed in cardiac and skeletal muscles, whereas TRB1 is expressed in the brain, liver and, kidneys and TRB2 in the hypothalamus and pituitary. In a child with typical features of hypothyroidism associated with borderline low thyroxine and high triiodothyronine levels, molecular studies identified a de novo, nonsense, heterozygous mutation in the TRA1 gene that was functionally deleterious. The mutation was a potent, dominant, negative inhibitor of wild-type thyroid hormone receptor action in vitro. Treatment with thyroxine resulted in partial responsiveness, but with negligible change in growth, intestinal motility, or heart rate, suggesting different sensitivity to thyroid hormone action [41]. This case report may point to a major role of TRA1 in bone and brain development.

Thyroid nodules and thyroid cancer

The incidence and mortality of pediatric differentiated thyroid carcinoma (DTC) is different in children compared to adults. These characteristics prompted the development of unique guidelines for children, issued by the American Thyroid Association (ATA), as regards thyroid nodules and thyroid cancer [42,43]. The guidelines provide insights concerning the role of ultrasound, fine needle aspiration cytology, and management of benign nodules, as well as suggestions for the evaluation, treatment, and follow-up of children with thyroid cancer [44]. Regarding thyroid cancer, the main recommendations include maintaining low disease-specific mortality by reducing potential complications from therapy, as well as pre- and post-operative surgery staging aimed at identifying patients who will benefit from aggressive therapy. Regarding thyroid nodules, annual thyroid physical examination is recommended in children who are at high risk for malignancy. Additional ultrasound imaging should be pursued in those with thyroid asymmetry, cervical lympadenopathy, or palpable nodes. Therapy should include LT4 suppression if compressive symptoms or history of radiation exposure exists.

Congenital adrenal hyperplasia

Defective adrenal steroidogenesis due to mutations in the CYP21A2 gene, encoding 21-hydroxylase, is the most frequent cause of congenital adrenal hyperplasia (CAH). A clinical practice guideline was released by the Endocrine Society in 2010 addressing several aspects of the disease, including screening, diagnosis, medical and, surgical treatment, as well as monitoring for complications [45]. There are two issues that deserve further attention.

Screening

The guideline recommends that screening for 21-hydroxylase deficiency should be incorporated into all newborn screening programs [45]. Both the timing of the screening test and gestational age should be taken into consideration when interpreting the results, as 17-OH progesterone levels vary widely during the first post-natal days, given that premature, sick, or stressed infants typically have higher levels.

Prenatal treatment

As for prenatal treatment for CAH, the panel of experts recommended that it should continue to be regarded as experimental and be applied only within the setting of clinical trials [45].

The administration of glucocorticoids during pregnancy to the mother with a fetus at high risk for CAH, in order to minimize the risk of virilization of the female genitalia of affected fetuses has been applied since the 1980s. Dexamethasone is used, as it is not deactivated by the placenta. To be effective, this treatment must be implemented before the initiation of autonomous fetal adrenal androgen synthesis (sixth to eighth weeks); in other words, as soon as the woman knows she is pregnant. Using this approach and taking into consideration that CAH is an autosomal recessive disorder and that half of these fetuses are male, seven out of eight high-risk pregnancies are treated unnecessarily. This has raised concerns regarding potential long-term complications in healthy fetuses. In fact, dexamethasone treatment during the first trimester has been associated with mild teratogenic effects and decreased birth weight (a cardiovascular risk factor), as well as emotional and cognitive disturbances [46], which, in some studies, appear to be sex-dimorphic [47].

Recent genomic advances have led to the development of non-invasive genetic techniques that minimize unnecessary dexamethasone exposure of unaffected fetuses. For example, by assessing fetal sex determination in maternal serum or using cell-free fetal DNA in maternal plasma, dexamethasone administration in women carrying a male fetus can be avoided [48].

Late onset or non-classic CAH

Non-classic forms of CAH are more prevalent, occurring in approximately 0.1–0.2% of the general Caucasian population. A study performed in 280 individuals with variable degrees of post-natal androgen excess disclosed that non-classical CAH has a variable phenotype, depending on age and gender and the presence of a classical mutation in one allele. A peak cutoff value of 17OHP post-ACTH lower than 30 nM (10 ng/ml) excludes the diagnosis, while some affected patients may present with baseline 17OHP concentrations baseline 17OHP < 6 nM(2 ng/ml) [49].

Disorders of sex development

Disorders of sex development (DSD) other than CAH are uncommon conditions in which there is discordance between chromosomal, gonadal, and anatomic sex. DSD has a prevalence of 0.1–0.5% of live births. In 2016, the Global DSD Update Consortium released an update on the diagnosis and care of individuals with DSD, in which clinical evaluation is updated concerning both infants with ambiguous genital development and adolescents with primary amenorrhea, progressive virilization, progressive clitoromegaly, and delayed or incomplete pubertal development. The update includes information on biochemical and genetic assessment and risk of germ cell tumor development, as well as psychosocial and psychosexual wellbeing. Patients with DSD have an increased risk of developing cancers of the germ cell lineage, malignant germ cell tumors, or germ cell cancer (GCC) compared to the

general population. During clinical management of patients with DSD, the GCC risk should be taken into account. The guidelines concerning GCC are the following. In males with gonadal dysgenesis (45,X/46,XY and 46,XY) and undescended testes, orchiopexy with biopsy, self-examination, and post-pubertal annual ultrasound are recommended. Post-pubertal biopsy will be conducted based on ultrasound and on the results of the first biopsy. If carcinoma in situ (CIS) evolves into gonadoblastoma, gonadectomy is recommended. In the case of ambiguous genitalia, the threshold for gonadectomy is lower. In females with gonadal dysgenesis (45,X/46,XY and 46,XY), bilateral gonadectomy is recommended at diagnosis. In patients with gonadal dysgenesis and unclear gender, the presence of ambiguous genitalia lowers the threshold for gonadectomy, while the presence of intact genitalia renders gonadectomy optional, depending on gender identity. In males with undervirilization (46,XY: partial androgen insensitivity syndrome-AIS, complete AIS, testosterone synthesis disorders) and undescended testes, orchiopexy with biopsy, self-examination, and post-pubertal annual ultrasound are recommended. Biopsy should be repeated at 10 years of age. If bilateral CIS is revealed, gonadectomy/irradiation is recommended. Gonadectomy is preferable in cases of testosterone supplementation or in order to avoid gynecomastia. In females with partial AIS and testosterone synthesis disorders, prepubertal gonadectomy is recommended. In females with complete AIS, post-pubertal gonadectomy or follow-up are recommended, given that GCC risk is low. In patients with partial AIS and testosterone synthesis disorders and unclear gender, bilateral biopsy is recommended [50].

Only a minority of DSD individuals will ever receive a definitive genetic diagnosis. The usefulness of DSD-genetic diagnostic tools, in which sex development genes are captured using RNA probes and undergo massively parallel sequencing, is highlighted, facilitating the genetic diagnosis of DSD individuals [51]. Diagnosing a DSD patient may represent a challenge, especially when DSD is associated with another condition or has an atypical presentation [52,53].

a) Over a quarter of cases of DSD registered in an international DSD registry have an additional condition, highlighting the need to search for novel genetic etiologies and more holistic care of affected persons;
b) XY DSD such as 5α-reductase deficiency should be investigated in élite young female athletes with primary amenorrhea and elevated testosterone levels.

Gender dysphoria/gender incongruence

Gender dysphoria or gender incongruence (according to the American Psychiatric Association and WHO ICD-11, respectively) refers to individuals who are not satisfied with their designated gender. Gender identity is not simply a psychosocial construct, but likely reflects a complex interplay of biological, environmental, and cultural factors. Mental health morbidities in gender-dysphoric youth often co-exist but are significantly diminished or resolved when such individuals are subject to a gender-affirming model of care, optimally delivered in a multidisciplinary clinical setting [54].

A recently released Endocrine Society Clinical Practice Guideline updates the current knowledge on the assessment and management of gender dysphoria. Compelling evidence supports the concept that biologic factors, in addition to environmental factors, may contribute to its development. Gender-affirming treatment is a multidisciplinary effort. The aims of hormone therapy are the following: suppression of endogenous sex hormone secretion determined by the person's genetic/gonadal sex and maintenance of sex hormone levels within the normal range for the person's affirmed gender. The recommendation for treatment of gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner stage G2/B2 is suppression with gonadotropin-releasing hormone agonists. Gender-affirming hormones may be added only after a multidisciplinary team assessment and confirmation of the persistence of gender dysphoria/gender incongruence, as well as the ascertainment of sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by the age 16 years. Although there may be compelling reasons to initiate sex hormone treatment prior to the age of 16, there is minimal published experience concerning treatment before 14 years of age. An expert multidisciplinary team composed of medical professionals and mental health professionals can manage the treatment of peripubertal youths and older adolescents and collaborate for decisions about gender-affirming surgery in older adolescents. Concerning adult gender-dysphoric/gender-incongruent individuals, maintenance of physiologic levels of gender-appropriate hormones and monitoring for known risks and complications are suggested. Whenever high doses of sex steroids are required to suppress endogenous sex steroids and/or when the individual is at a more advanced age, gonadectomy along with a reduction of sex steroid treatment are recommended.

When surgical removal is incomplete, both transgender males (female to male) and transgender females (male to female) should be monitored for reproductive organ cancer risk. Persistent monitoring of adverse effects of sex steroids is highly recommended, while hormone treatment should be administered with caution in individuals with concurrent conditions that may not benefit from the physical changes associated with this treatment [55].

Bone and calcium metabolism

Given the potentially toxic effects of vitamin D excess, the recommendations for the optimal dose of vitamin D supplementation for the prevention of rickets are still being debated. Along these lines, the investigation of the molecular basis of idiopathic infantile hypercalcemia, which is characterized by severe hypercalcemia, failure to thrive, vomiting, dehydration, and nephrocalcinosis revealed that defects in CYP24A1, which encodes 25-hydroxyvitamin D 24-hydroxylase, are causative for idiopathic infantile hypercalcemia and are a genetic risk factor for the development of a serious adverse effects of generally advocated vitamin D prophylaxis [56].

Inorganic pyrophosphate accumulates extracellularly, leading to rickets or osteomalacia. Hypophosphatasia results from mutations in the gene for the tissue-non-specific isozyme of alkaline phosphatase (TNSALP). Severely affected babies often die from respiratory insufficiency due to a progressive chest deformity or have persistent bone disease. Long-term administration of ENB-0040, a bone-targeted, recombinant human TNSALP, improves skeletal abnormalities and pulmonary function of patients with hypophosphatasia and thus appears to be a potential enzyme-replacement therapy for this disorder [57].

Regulation of bone remodeling by an adipocyte-derived hormone means that the bones may exert a feedback control of energy homeostasis. In this regard, it has been shown that osteocalcin can improve glucose tolerance in vivo and can stimulate cyclinD1 and insulin expression in beta-cells ex vivo as well as adiponectin in adipocytes [58]. The skeleton, through osteocalcin, regulates not only glucose homeostasis but male fertility as well. Osteocalcin binds to a G protein-coupled receptor expressed in the Leydig cells of the testes, regulating in a CREB-dependent manner the expression of enzymes that are required for testosterone synthesis, thereby promoting germ cell survival [59].

Growth disorders

The overall safety profile of rhGH is favorable, but careful monitoring for the presence of certain conditions is important both during and after therapy, including children with prior malignancies who received radiation therapy and children with short stature, associated with specific syndromes, who may become more insulin resistant [60].

The effectiveness of rhGH in final height appears to be similar in patients with short stature homeobox-containing gene (SHOX) deficiency and in girls with Turner's syndrome. However, the study reporting these results was biased because it was ended too early to allow all patients to reach final height [61].

Clinical practice guidelines for rhGH and IGF-I treatment in children and adolescents with GH deficiency, idiopathic short stature, and IGF-I deficiency, and for the care of patients with Turner syndrome have been released, as well as the results of a first international consensus statement on the diagnosis and management of Silver-Russell syndrome. Updated guidelines concerning the use rhGH were published in 2016 by the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society [62]. The guidelines focused on the differential diagnosis among idiopathic short stature (ISS), GH deficiency (GHD), and primary IGF-I deficiency (PIGFD). The guidelines were developed following the GRADE approach (Grading of Recommendations, Assessment, Development, and Evaluation), providing recommendations for the clinical management of children and adolescents with growth failure, including IGF-I therapy according to the rGH guidelines for the first time. The taskforce suggests that the recommendations can be applied in clinical practice with consideration of the best available evidence and taking the individual risks and benefits into account.

Turner syndrome affects 25–50 per 100,000 females and can involve multiple organs through all stages of life, necessitating a multidisciplinary approach. Updated guidelines were released in 2017 concerning important areas in Turner's syndrome care including: (1) diagnostic and genetic issues, (2) growth and development during childhood and adolescence, (3) congenital and acquired cardiovascular disease, (4) transition and adult care, and (5) other comorbidities and neurocognitive issues. The project was initiated by the European Society of Endocrinology and the Pediatric Endocrine Society, in collaboration with the European Society for Paediatric Endocrinology, the Endocrine Society, the European Society of Human Reproduction and Embryology, the American Heart Association, the Society for Endocrinology, and the European Society of Cardiology. The guidelines have been formally endorsed by the European Society of Endocrinology, the Pediatric Endocrine Society, the European Society for Paediatric Endocrinology, the European Society of Human Reproduction and Embryology, and the Endocrine Society [63].

The first International Consensus Statement including recommendations for the clinical diagnosis, investigation, and management of patients with Silver-Russell syndrome (SRS) was published in 2017. SRS is an imprinting disorder that causes prenatal and post-natal growth retardation. The benefits of treating patients with SRS with growth hormone include an improvement of body composition, motor development and appetite, a reduction of hypoglycemia, and an increase in height. Specific issues, such as the development of premature adrenarche and early and rapid puberty and insulin resistance, are addressed. Gonadotropin-releasing hormone

analogues are recommended to delay pubertal progression in order to preserve adult height potential [64].

Recently, phase II studies in prepubertal, treatment-naïve GHD children comparing the efficacy and safety of a long-acting recombinant GH of sustained release (weekly administration) to those of daily rhGH are yielding positive results. This outcome supports advancement to phase III development [65].

Heterozygous mutations in the ACAN gene coding for the proteoglycan aggrecan, a main component of the cartilage matrix, have been associated with growth defects, ranging from ISS to severe skeletal dysplasias. Genetic screening confirmed heterozygous mutations in ACAN as a major cause of ISS [66]. Mutations in ACAN result in a broad phenotypic spectrum of non-lethal skeletal dysplasias, including spondyloepimetaphyseal dysplasia, spondyloepiphyseal dysplasia, familial osteochondritis dissecans, and various undefined short-stature syndromes associated with accelerated bone maturation. It is thus evident that the aggrecanopathies are an evolving phenotypic spectrum of human genetic skeletal diseases [67].

Conclusions

Although considerable progress has been made in the field of pediatric endocrinology, there is still a long way to go as regards exploration for and uncovering of novel avenues, mainly in the domains of genetics and epigenetics. Such research will enable the discovery of as yet unknown mechanisms of disease and, thereby, the development of new and more specific interventions. In the coming years, it will also be crucial to build upon the advances of the last decade, with the willingness, if necessary, to change paradigms and develop new approaches to disease. A prime example of the latter is the ever greater application of personalized medicine, wherein the diagnosis and management of specific disorders will be decided upon on an individual basis, thus ultimately increasing the chances for success.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

References

1. Oron T, Lebenthal Y, de Vries L, Yackobovitch-Gavan M, Phillip M, Lazar L (2012) Interrelationship of extent of precocious adrenarche in appropriate for gestational age girls with clinical outcome. J Pediatr 160:308–313
2. Deng X, Li W, Luo Y, Liu S, Wen Y, Liu Q (2017) Association between small fetuses and puberty timing: a systematic review and meta-analysis. Int J Environ Res Public Health 14(11)
3. Uçar A, Yackobovitch-Gavan M, Erol OB et al (2014) Associations of size at birth and postnatal catch-up growth status with clinical and biomedical characteristics in prepubertal girls with precocious adrenarche: preliminary results. J Clin Endocrinol Metab 99:2878–2886
4. de Zegher F, Reinehr T, Malpique R, Darendeliler F, López-Bermejo A, Ibáñez L (2017) Reduced prenatal weight gain and/or augmented postnatal weight gain precedes polycystic ovary syndrome in adolescent girls. Obesity 25:1486–1489
5. de Zegher F, GarcíaBeltrán C, López-Bermejo A, Ibáñez L (2018) Metformin for rapidly maturing girls with central adiposity: less liver fat and slower bone maturation. Horm Res Paediatr 89:136–140
6. Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, de Zegher F (2011) Early metformin therapy (age 8–12 years) in girls with precocious pubarche to reduce hirsutism, androgen excess, and oligomenorrhea in adolescence. J Clin Endocrinol Metab 96:E1262–E1267
7. Abreu AP, Dauber A, Macedo DB et al (2013) Central precocious puberty caused by mutations in the imprinted gene MKRN3. N Engl J Med 368:2467–2475
8. Hagen CP, Sørensen K, Mieritz MG, Johannsen TH, Almstrup K, Juul A, 2015 Circulating MKRN3 levels decline prior to pubertal onset and through puberty: a longitudinal study of healthy girls. J Clin Endocrinol Metab100:1920–1926
9. Busch AS, Hagen CP, Almstrup K, Juul A (2016) Circulating MKRN3 levels decline during puberty in healthy boys. J Clin Endocrinol Metab 101:2588–2593
10. Silverman LA, Neely EK, Kletter GB et al (2015) Long-term continuous suppression with once-yearly histrelin subcutaneous implants for the treatment of central precocious puberty: a final report of a phase 3 multicenter trial. J Clin Endocrinol Metab 100:2354–2363
11. Lazar L, Meyerovitch J, de Vries L, Phillip M, Lebenthal Y (2014) Treated and untreated women with idiopathic precocious puberty: long-term follow-up and reproductive outcome between the third and fifth decades. Clin Endocrinol 80:570–576
12. Lazar L, Lebenthal Y, Yackobovitch-Gavan M, et al, 2015 Treated and untreated women with idiopathic precocious puberty: BMI evolution, metabolic outcome, and general health between third and fifth decades. J Clin Endocrinol Metab100:1445–1451
13. Howard SR, Guasti L, Ruiz-Babot G et al (2016) IGSF10 mutations dysregulate gonadotropin-releasing hormone neuronal migration resulting in delayed puberty. EMBO Mol Med 8:626–642
14. Howard SR, Guasti L, Poliandri A et al (2018) Contributions of function-altering variants in genes implicated in pubertal timing and body mass for self-limited delayed puberty. J Clin Endocrinol Metab 103:649–659
15. Ibáñez L, Oberfield SE, Witchel S et al (2017) An international consortium update: pathophysiology, diagnosis, and treatment of polycystic ovarian syndrome in adolescence. Horm Res Paediatr 88:371–395
16. Anderson AD, Solorzano CM, McCartney CR (2014) Childhood obesity and its impact on the development of adolescent PCOS. Semin Reprod Med 32:202–213
17. Lass N, Kleber M, Winkel K, Wunsch R, Reinehr T (2011) Effect of lifestyle intervention on features of polycystic ovarian syndrome, metabolic syndrome, and intima-media thickness in obese adolescent girls. J Clin Endocrinol Metab 96:3533–3540
18. Ibáñez L, del Río L, Díaz M et al (2017) Normalizing ovulation rate by preferential reduction of hepato-visceral fat in adolescent girls with polycystic ovary syndrome. J Adolesc Health 61:446–453
19. Levy-Marchal C, Arslanian S, Cutfield W et al (2010) Insulin resistance in children: consensus, perspective, and future directions. J Clin Endocrinol Metab 95:5189–5198
20. Gluckman PD, Hanson MA, Cooper C, Thornburg KL (2008) Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 359:61–73

21. Voerman E, Jaddoe VW, Franco OH, Steegers EA, Gaillard R (2017) Critical periods and growth patterns from fetal life onwards associated with childhood insulinlevels. Diabetologia 60:81–88
22. Ogden CL, Carroll MD, Kit BK, Flegal KM (2014) Prevalence of childhood and adult obesity in the United States, 2011–2012. 311: 806–814
23. Preventive Services Task Force US, Grossman DC, Bibbins-Domingo K, Curry SJ et al (2017) Screening for obesity in children and adolescents: US Preventive Services Task Force recommendation statement. JAMA 317:2417–2242
24. Reinehr T, Lass N, Toschke C, Rothermel J, Lanzinger S, Holl RW (2016) Which amount of BMI-SDS reduction is necessary to improve cardiovascular risk factors in overweight children? J Clin Endocrinol Metab 101:3171–3179
25. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C (2005) Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ 331:929
26. Druet C, Stettler N, Sharp S et al (2012) Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. Paediatr Perinat Epidemiol 26:19–26
27. Elks CE, Heude B, de Zegher F et al (2014) Associations between genetic obesity susceptibility and early postnatal fat and lean mass: an individual participant meta-analysis. JAMA Pediatr 168:1122–1130
28. Díaz M, García C, Sebastiani G, de Zegher F, López-Bermejo A, Ibáñez L (2017) Placental and cord blood methylation of genes involved in energy homeostasis: association with fetal growth and neonatal body composition. Diabetes 66:779–784
29. Dabelea D, Mayer-Davis EJ, Saydah S et al (2009) Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to. JAMA 311:1778–1786
30. Onkamo P, Väänänen S, Karvonen M, Tuomilehto J (1999) Worldwide increase in incidence of type I diabetes—the analysis of the data on published incidence trends. Diabetologia 42:1395–1403
31. Mayer-Davis EJ, Lawrence JM, Dabelea D et al (2017) Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. N Engl J Med 376:1419–1429
32. Dabelea D, Stafford JM, Mayer-Davis EJ et al (2017) Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA 317:825–835
33. Chrysis D, Efthymiadou A, Mermigka A, Kritikou D, Spiliotis BE (2017) Osteoprotegerin, RANKL, ADMA, and Fetuin-A serum levels in children with type I diabetes mellitus. Pediatr Diabetes 18:277–282
34. Dabelea D, Mayer-Davis EJ, Lamichhane AP et al (2008) Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth. Diabetes Care 31:1422–1426
35. van der Steen I, van Albada ME, Mohnike K et al (2018) A multicenter experience with long-acting somatostatin analogues in patients with congenital hyperinsulinism. Horm Res Paediatrics 89: 82–89
36. Senniappan S, Alexandrescu S, Tatevian N et al (2014) Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. N Engl J Med 370:1131–1137
37. Maynika V Rastogi and Stephen H LaFranchi (2010) Congenital hypothyroidism Orphanet J Rare Dis. 1186/1750-1172-5-17
38. Léger L, Olivieri A, Donaldson M et al (2014) European Society for Paediatric Endocrinology Consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab 99:363–384
39. Mengreli C, Kanaka-Gantenbein C, Girginoudis P (2010) Screening for congenital hypothyroidism: the significance of threshold limit in false-negative results. J Clin Endocrinol Metab 95:4283–4290
40. Wasniewska M, Salerno M, Cassio A et al (2009) Prospective evaluation of the natural course of idiopathic subclinical hypothyroidism in childhood and adolescence. Eur J Endocrinol 160:417–422
41. Bochukova E, Schoenmakers N, Agostini M et al (2012) A mutation in the thyroid hormone receptor alpha gene. N Engl J Med 366: 243–249
42. Gupta A, Ly S, Castroneves LA, Frates MC et al (2013) A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. J Clin Endocrinol Metab 98:3238–3245
43. Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE (2009) Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. J Surg Res 156:167–172
44. Francis GL, Waguespack SG, Bauer AJ, American Thyroid Association Guidelines Task Force et al (2015) Management guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid 25:716–759
45. Speiser PW, Azziz R, Baskin LS et al (2010) Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 95: 4133–4160
46. Miller WL, Witchel SF (2013) Prenatal treatment of congenital adrenal hyperplasia: risks outweigh benefits. Am J Obstet Gynecol 208:354–359
47. Wallensteen L, Zimmermann M, Thomsen Sandberg M, Gezelius A, Nordenström A, Hirvikoski T, Lajic S (2016) Sex-dimorphic effects of prenatal treatment with dexamethasone. J Clin Endocrinol Metab 101:3838–3846
48. Tardy-Guidollet V, Menassa R, Costa JM et al (2014) New management strategy of pregnancies at risk of congenital adrenal hyperplasia using fetal sex determination in maternal serum: French cohort of 258 cases (2002–2011). J Clin Endocrinol Metab 99: 1180–1188
49. Livadas S, Dracopoulou M, Dastamani A et al (2015) The spectrum of clinical, hormonal and molecular findings in 280 individuals with nonclassical congenital adrenal hyperplasia caused by mutations of the CYP21A2 gene. Clin Endocrinol 82:543–549
50. Lee PA, Nordenström A, Houk CP et al (2016) Global DSD Update Consortium. Global disorders of sex development update since 2006: perceptions, approach, and care. Horm Res Paediatr 85: 158–180
51. Arboleda VA, Lee H, Sánchez FJ et al (2013) Targeted massively parallel sequencing provides comprehensive genetic diagnosis for patients with disorders of sex development. Clin Genet 83:35–43
52. Cox K, Bryce J, Jiang J et al (2014) Novel associations in disorders of sex development: findings from the I-DSD Registry. J Clin Endocrinol Metab 99:E348–E355
53. Fénichel P, Paris F, Philibert P et al (2013) Molecular diagnosis of 5α-reductase deficiency in 4 elite young female athletes through hormonal screening for hyperandrogenism. J Clin Endocrinol Metab 98:E1055–E1059
54. Rosenthal SM (2014) Approach to the patient: transgender youth: endocrine considerations. J Clin Endocrinol Metab 99:4379–4389
55. Hembree WC, Cohen-Kettenis PT, Gooren L et al (2017) Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 102:3869–3903
56. Schlingmann KP, Kaufmann M, Weber S et al (2011) Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med 365:410–421
57. Whyte MP, Greenberg CR, Salman NJ et al (2012) Enzyme-replacement therapy in life-threatening hypophosphatasia. N Engl J Med 366:904–913
58. Lee NK, Sowa H, Hinoi E et al (2007) Endocrine regulation of energy metabolism by the skeleton. Cell 130:456–469

59. Oury F, Sumara G, Sumara O et al (2011) Endocrine regulation of male fertility by the skeleton. Cell 144:796–809
60. Bell J, Parker KL, Swinford RD, Hoffman AR, Maneatis T, Lippe B (2010) Long-term safety of recombinant human growth hormone in children. J Clin Endocrinol Metab 95:167–177
61. Blum WF, Ross JL, Zimmermann AG et al (2013) GH treatment to final height produces similar height gains in patients with SHOX deficiency and Turner syndrome: results of a multicenter trial. J Clin Endocrinol Metab 98:E1383–E1392
62. Grimberg A, DiVall SA, Polychronakos C, Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society et al (2016) Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr 86:361–397
63. Gravholt CH, Andersen NH, Conway GS, International Turner Syndrome Consensus Group et al (2017) Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol 177:G1–G70
64. Wakeling EL, Brioude F, Lokulo-Sodipe O et al (2017) Diagnosis and management of Silver-Russell syndrome: first international consensus statement. Nat Rev Endocrinol 13:105–124
65. Chatelain P, Malievskiy O, Radziuk K, TransCon GH Working Group et al (2017) A randomized phase 2 study of long-acting TransCon GH vs daily GH in childhood GH deficiency. J Clin Endocrinol Metab 102:1673–1682
66. Hauer NN, Sticht H, Boppudi S et al (2017) Genetic screening confirms heterozygous mutations in ACAN as a major cause of idiopathic short stature. Sci Rep 7:12225
67. Gibson BG, Briggs MD (2016) The aggrecanopathies; an evolving phenotypic spectrum of human genetic skeletal diseases. Orphanet J Rare Dis 11:86