Title: Peripheral Precocious Puberty including congenital adrenal hyperplasia: *causes, consequences, management and outcomes*

Authors:

1- Nadine G. Haddad, MD
Associate Professor of Pediatrics
Riley Hospital for Children
705 Barnhill Dr, Rm 5960
Indianapolis, IN 46202
Phone: + 1(317)944-3889
Fax: +1(317)944-3882
Email: nhaddad@iu.edu

2- Erica A. Eugster, MD
Professor of Pediatrics
Riley Hospital for Children
705 Barnhill Dr, Rm 5960
Indianapolis, IN 46202
Phone: + 1(317)944-3889
Fax: +1(317)944-3882
Email: eeugster@iu.edu

Corresponding author: Nadine G. Haddad, MD

This is the author's manuscript of the article published in final edited form as:

Haddad, N. G., & Eugster, E. A. (2019). Peripheral Precocious Puberty including congenital adrenal hyperplasia: causes, consequences, management and outcomes. Best Practice & Research Clinical Endocrinology & Metabolism. https://doi.org/10.1016/j.beem.2019.04.007

Abstract

Peripheral precocious puberty results from peripheral production of sex steroids independent of activation of the hypothalamic-pituitary gonadal axis. It is much less common than central precocious puberty. Causes are variable and can be congenital or acquired. In this review, we will discuss the diagnosis and management of the most common etiologies including congenital adrenal hyperplasia, McCune Albright syndrome, familial male-limited precocious puberty, and adrenal and gonadal tumors.

Key words

Peripheral precocious puberty

Congenital adrenal hyperplasia

McCune Albright syndrome

Familial male-limited precocious puberty

Aromatase inhibitors

Adrenal tumors

Gonadal tumors

Introduction

Peripheral precocious puberty (PPP) refers to conditions in which early puberty occurs as a result of sex steroid production from gonadal and extra gonadal sources independent of gonadotropin stimulation. PPP is much less common than CPP, and may be congenital or acquired. Unlike in CPP, the type of secondary sexual development, rate of progression and sequence of pubertal events in PPP may be strikingly different from that seen in normally-timed puberty.

In this review, we will describe the most frequently encountered etiologies of PPP including congenital adrenal hyperplasia (CAH), McCune Albright syndrome (MAS), Familial male-limited precocious puberty (FMPP), and sex steroid secreting tumors.

1- Congenital Adrenal Hyperplasia:

CAH is a family of autosomal recessive diseases of abnormal cortisol biosynthesis, which is commonly associated with disordered puberty (1).

Several enzymatic defects are associated with CAH and are highlighted in Figure 1. Clinical manifestations depend on the enzyme involved, type of mutation and the hormone that is overproduced or deficient. Of all causes of CAH, 21 hydroxylase (21OHase) deficiency is the most common followed by 11 beta hydroxylase (11OHase) deficiency, and 3 beta hydroxysteroid dehydrogenase (3ßHSD) deficiency. Other less common forms of CAH include p450oxidoreductase deficiency, 17hydroxylase deficiency and lipoid CAH (StAR deficiency). In this review, we will focus on CAH due to 21OHase deficiency which is the most common cause of PPP.

A- CAH due to 21OHase deficiency

The most common cause of CAH, 21OHase deficiency accounts for more than 90% of affected individuals (2, 3), and has a worldwide incidence of 1 in ~15,000 livebirths. CAH due to 21OHase deficiency results from alterations in the highly homologous p450c21 genes which consist of an inactive pseudogene (*CYP21A1* or *CYP21P*) and an active gene (*CYP21A2* or *CYP21*), both located in a small

region on chromosome 6p21.3 (4, 5). Approximately 75% of mutations are due to recombination events between the inactive and active genes, resulting in gene conversions. However, a multitude of other molecular genetic abnormalities involving *CYP21A* also occur.

The 21 OHase enzyme is involved in the cortisol and mineralocorticoid pathways, and propels the conversion of 17 hydroxyprogesterone to 11 deoxycortisol and progesterone to deoxycorticosterone. Cortisol deficiency stimulates ACTH secretion which in turn drives the production of androgens (DHEA and androstenedione) due to a build-up of precursors proximal to the block in the glucocorticoid pathway. These 2 androgens are converted to testosterone and cause signs of virilization which is the clinical hallmark of CAH due to 21 OHase deficiency.

The clinical manifestations of 21OHase deficiency may be broadly divided into 3 different categories: the classic salt wasting, the classic non salt wasting or simple virilizing and the nonclassic form. Classic 21OHase deficiency results from a combination of 2 severe gene mutations, whereas individuals with the nonclassic form are compound heterozygotes, having one severe mutation and one mild mutation or are homozygous with 2 mild gene mutations. The majority of children with classic CAH are salt wasting. The nonclassic form is one of the most common autosomal recessive diseases, with a higher prevalence in certain ethnic groups specifically Eastern European Jews, Yugoslavs, Mediterranean and Hispanics (6).

Clinical manifestations:

In line with its molecular genetic heterogeneity, the phenotype of individuals with 21OHase deficiency exists within a broad spectrum. Females with the classic form present with ambiguous genitalia with variable degrees of virilization, ranging from isolated clitoromegaly to male-appearing external genitalia but without palpable testes, as seen in figure 2. Internal genitalia include normal ovaries and uterus. Under the effect of excess androgens, the urethra and vagina may share a common channel internally resulting in a single perineal opening known as a urogenital sinus. Males with the salt-wasting form who are not identified by neonatal screening typically present with failure to thrive, and an adrenal crisis between 1 and 2 weeks of life. Their external genitalia appear normal, with the exception of some skin hyperpigmentation.

Postnatally, children may develop pubic and axillary hair, acne, and early adult body odor. If inadequately controlled, the excess androgens can cause rapid linear growth and advancement in skeletal maturation which may eventually impair height potential and cause short stature. A meta-analysis from 18 centers showed that the mean adult height (AH) of patients with classic CAH was 1.4 standard deviations (10 cm) below the population mean (7). Secondary CPP may complicate CAH and further compromise AH (8) particularly in patients with poor control.

During adolescence and adulthood, affected girls and women may develop hirsutism, significant acne, irregular menses, amenorrhea, and infertility, in a picture similar to polycystic ovary syndrome (9, 10). Additional signs of androgen excess such as increased muscle mass and deepening of the voice may develop, particularly in the setting of non-compliance. Decreased fertility resulting from chronic anovulation and endometrial dysfunction have been described in women with classic and nonclassic CAH owing to excess androgen secretion which alters the hypothalamic pituitary gonadal axis and affects ovarian function directly (11). Similarly, low fertility rates are described in men with CAH, with testicular adrenal rest tumors (TART) being the most common cause (12, 13). TARTs are benign tumors resembling adrenocortical tissue, which are typically found in the rete testis and thought to cause mechanical oligospermia or azoospermia via obstruction of the terminal seminiferous tubules. There is evidence to suggest that cells in TARTs derive from totipotent embryonic cells that resemble fetal Leydig cells. These cells have ACTH and LH receptors and stimulation by both hormones at various stages in life can lead to TART formation (14).

Diagnosis

Girls and boys with nonclassic CAH due to 21 OHase deficiency may present in childhood with premature pubarche and other signs of androgen excess. Young women may present with hirsutism and menstrual irregularities.

A very high random serum 17-hydroxyprogesterone level of >3500 ng/dL and typically > 10,000 ng/dl is diagnostic of classic CAH. Lower levels are seen in nonclassic forms with a 17-hydroxyprogesterone level

of >1500 ng/dl being diagnostic (1, 15). In patients with borderline results, an ACTH stimulation test may be necessary.

In children with clinical signs of CPP, a GnRH stimulation test may be necessary to confirm this diagnosis.

Treatment

- The treatment of 21OHase deficiency is aimed at suppressing adrenal androgen production while avoiding overtreatment with glucocorticoids which may lead to decreased linear growth. While hydrocortisone is believed to have the least deleterious effect on growth, a wide range of individual sensitivity to different forms of glucocorticoids has been demonstrated (16). Children with salt wasting CAH also require mineralocorticoid replacement as well as salt supplementation during the first few years of life.

- Although early genital surgery is an area of controversy (17), vaginoplasty and clitoral recession are often opted for by parents of girls with severe manifestations of classic CAH (18). With extremely rare exceptions, a female sex assignment is considered standard of care (2). While a female gender identity is the norm, girls with classic 21OHase deficiency exhibit an increase in “boy-typical” behavior, toy preferences and cognitive abilities (19).

- Children with nonclassic CAH may require treatment with a glucocorticoid if they have significant signs of virilization or bone age (BA) advancement.

- Intensifying glucocorticoid treatment is the mainstay medical treatment for men or women with CAH and impaired fertility.

- In children with evidence of CPP, treatment with a GnRH analog (GnRHa) may be added to improve AH. Several small case series of children with CAH and CPP showed regression in breast development and testicular volume, decreased BA advancement and linear growth velocity and improved growth potential with GnRHa treatment (8, 20). Treatment should be started early and appears to be more beneficial in those whose BA is not significantly advanced (21).

- Although not considered standard of care, a few small studies have suggested that the addition of growth hormone (GH) treatment to a GnRHa may further augment preservation of height potential in these patients (22, 23).

2- McCune Albright syndrome

McCune Albright syndrome (MAS) is a rare cause of PPP, and is a sporadic condition caused by post-zygotic activating mutations in the *GNAS1* gene on chromosome 20 (24). The gene encodes the alpha subunit of G-protein (Gsα), a receptor mediator which stimulates intracellular cyclic AMP formation. Activating mutations lead to autonomous hyperfunction of several endocrine and non-endocrine tissues (25). In addition to PPP, endocrine manifestations that can be present in variable combinations in MAS include growth hormone excess, hyperthyroidism, cortisol excess, hyperprolactinemia and hypophosphatemia.

PPP is the most common endocrine manifestation, and occurs more frequently in girls in whom it is almost invariably the presenting feature of the disease (26).

Classically described as the triad of PP, fibrous dysplasia of bones, and café-au-lait macules, MAS is now recognized as a heterogenous condition with a spectrum of findings resulting from variable tissue distribution of the mutation. The café au lait macules in MAS have irregular borders (coast of Maine) in contrast to the café au lait macules of neurofibromatosis which have smooth borders (coast of California). They typically follow the developmental lines of Blaschko and do not cross the midline, as seen in figure 3.

PPP in girls results from the production of high levels of estrogens by autonomously functioning unilateral ovarian cysts.

Clinical signs resulting from estrogen exposure include breast development, estrogenization of the vaginal mucosa, accelerated linear growth and vaginal bleeding which results from withdrawal of estrogen when the cyst resolves. Vaginal bleeding without breast development may be the only manifestation, which can occur if a cyst rapidly develops and involutes.

The clinical course of girls with MAS and PPP is variable with some girls experiencing vaginal bleeding once with no further episodes, and others having recurrent cysts at unpredictable intervals. Girls with recurrent cysts may experience accelerated linear growth and BA advancement leading to a decrease in final AH. Therefore a period of observation after a first episode of bleeding is necessary, and treatment should be reserved for those with a progressive form of PPP. Secondary CPP may complicate the course of the disease especially in girls with a significantly advanced BA. The differentiation of CPP from PPP based on clinical features may be difficult in this instance, and a GnRH stimulation test may be necessary. An LH peak of 4-6 mIU/ml in response to GnRH stimulation confirms CPP.

Many girls with MAS continue to have irregular menstrual bleeding in adulthood due to persistent autonomous ovarian function. However, long term data suggest that these women have successful spontaneous pregnancies despite a longer than average time to conception (27). Menstrual regulation can be achieved with combined oral contraceptive pills or with progestin only containing pills or intrauterine device.

PPP occurs less commonly in boys compared to girls. In a study of 54 males with MAS, PPP was present in 21% of patients resulting from constitutive activation of Gsα leading to increased production of testosterone. The most common histopathological finding was Leydig cell hyperplasia, which can be unilateral. Germ cell tumor was diagnosed in one patient. Abnormal ultrasound findings were present in 81% of patients, and included hyperechoic lesions (49%), hypoechoic lesions (30%), microlithiasis (30%), heterogeneity (47%) and focal calcifications (11%). These findings suggest that while PPP is not common in boys with MAS, the incidence of gonadal pathology is similar between boys and girls (28).

Macroorchidism is commonly seen and was reported in 44% of patients with MAS, half of whom were children, and was more commonly bilateral (28). The presence of macroorchidism in children with MAS poses a special diagnostic challenge especially in the presence of signs of puberty, as it can result from CPP or PPP. Alternatively, Sertoli-cell only *GNAS1* mutations have been reported as a cause of macroorchidism in boys with MAS, further complicating the diagnostic process (29). Additional testing in the form of a GnRH stimulation test may be necessary in this setting. The co-existence of PPP and GH

excess can result in particularly rapid linear growth and coarsening of the facial features. Thus, it is important to maintain vigilance regarding additional potential manifestations of MAS during routine follow up.

Testicular ultrasound and serial exams are recommended for all males with MAS, with close observation and serial imaging if lesions without local invasions are noted. Surgical intervention should be reserved for palpable, rapidly growing or locally invasive lesions due to risk for malignant degeneration of some lesions (28). While microlithiasis is a common finding in boys with MAS, it is unclear if it leads to increased neoplastic transformation (30).

Diagnosis

In girls with clinical features suggestive of MAS, an elevated serum estradiol level and suppressed gonadotropins confirms the diagnosis of PPP. A pelvic ultrasound typically reveals a large unilateral ovarian cyst. Occasionally, a hemorrhagic cyst may be mistaken for a tumor leading to unnecessary oophorectomy (31).

Once the diagnosis of MAS is made, a bone scan should be obtained to evaluate for associated fibrous dysplasia lesions, and laboratory testing should be performed to assess for other associated endocrine hyperfunction.

While genetic testing for *GNAS1* gene mutations is commercially available, the yield is low due to the mosaic distribution of the mutation and the fact that it may be limited to specific tissues and is frequently not detected in peripheral blood. Thus, the diagnosis of MAS remains a clinical one.

Treatment

- Surgical resection of the ovarian cyst or oophorectomy is not recommended for the treatment of PPP in girls with MAS, due to a negative impact on fertility and the potential for recurrence of cysts in remaining ovarian tissue.

- Medical treatment should be reserved for girls with recurrent ovarian cysts associated with frequent episodes of vaginal bleeding and advanced BA leading to compromised AH, keeping in mind that height predictions and assessment of linear growth can be complicated by the concomitant presence of hyperthyroidism, GH excess, or fibrous dysplasia . Additionally, extreme fluctuations in estradiol levels are common and the BA can advance rapidly, adding to the challenge of the management of this complex condition. Therefore, the decision to treat should be individualized and a period of close observation for frequency of menstrual bleeding, linear growth velocity and rate of BA advancement may be necessary initially, and periodic surveillance for associated endocrinopathies that can affect growth will be important.

- Various pharmacologic interventions have been studied. Historically, progestins such as medroxyprogesterone acetate and anti-androgens such as cyproterone acetate were attempted but found to be ineffective (Table 1). Ketoconazole, a nonspecific p450 inhibitor of adrenal and gonadal steroidogenesis has also been tried. While it results in cessation of menses and regression of pubertal signs (32), there are concerns about its long term safety and potential for adrenal insufficiency and hepatotoxicity (33).

- More recent medical interventions have been aimed at decreasing estrogen production with aromatase inhibitors (AIs) or blocking the effect of estrogens at the end organ with estrogen receptor modulators.

- AIs are a class of nonsteroidal competitive inhibitors of the p450 aromatase enzyme which catalyze the conversion of androgens to estrogens .While the first and second generation agents testolactone and fadrozole were tried in girls with MAS, they were ineffective (34, 35). Third generation agents such as anastrozole and letrozole have a higher potency and are better tolerated compared to earlier generation AIs. However, only letrozole has been demonstrated to have efficacy in the treatment of MAS (36-38). In a pilot study of 9 girls treated with letrozole, linear growth and BA advancement rates significantly decreased while menstrual bleeding ceased or decreased in frequency. However, an increase in mean ovarian volume and in cyst

size was noted, and one girl had a large ovarian cyst which resulted in torsion (38). Long term outcomes of 28 girls including the 9 girls from the initial pilot study treated with letrozole for up to 10 years were published (37). Results showed a significant improvement in PAH, no adverse events, and no changes in uterine or ovarian volumes.

- Tamoxifen was investigated in a prospective multicenter study of 25 girls with PPP and MAS treated for 1 year. Episodes of vaginal bleeding decreased, linear growth slowed, and rates of skeletal maturation decreased. However, an increase in uterine volume was noted (39). In a retrospective study of 8 girls treated with tamoxifen for 3-8 years and followed for a mean period of 8.3 years, vaginal bleeding ceased and PAH increased (40). Reassuringly, no alteration in uterine volumes or endometrial thickness was noted.

- Fulvestrant, a pure estrogen receptor antagonist, was studied in 30 girls with PPP related to MAS and found to be moderately effective and safe (41). However, the requirement for intramuscular injections is a distinct drawback to its use.

- Table 1 summarizes the efficacy and safety of the different pharmacologic agents used for the treatment of PPP in girls with MAS.

- Given the rarity of boys with MAS and PPP, treatment information is derived from case reports. Similar to the treatment approach in other forms of PPP in boys, the combination of anastrozole and the competitive androgen blocker bicalutamide has been reported and appears to be a promising treatment option for this rare condition (42). This combination treatment will be discussed further in the FMPP section.

3- <u>Familial male limited precocious puberty</u>

FMPP or testotoxicosis is a rare disorder caused by an activating mutation of the LH receptor resulting in autonomous Leydig cell secretion of testosterone, independent of gonadotropin stimulation (43, 44). Mutations can be de novo or inherited in an autosomal dominant fashion. Characteristically, patients have an elevated testosterone and suppressed gonadotropins and the clinical phenotype is limited to males.

Affected boys typically present before the age of 4 years with signs of virilization. Mild testicular enlargement is usually present. If left untreated, affected individuals will achieve significantly shorter AHs than expected for their genetic potential. Although pubertal progression is the norm, a case of FMPP characterized by intermittent spontaneous remission has also been reported (45).

Secondary CPP can develop and complicate the picture, especially in boys with a significantly advanced BA (46).

Despite reported oligospermia in a few men with FMPP, most retain normal fertility (47-49). Reports of one man with a seminoma (50) and a child with testicular nodular hyperplasia (51) should raise awareness of the possibility of the development of tumors in FMPP.

Treatment

Different pharmacological regimens have been used to treat boys with FMPP. Results of studies of medical treatment in FMPP are summarized in table 2.

- Cyproterone acetate and medroxyprogesterone acetate were historically used in boys with FMPP but were minimally effective in preserving AH (52).

- In contrast, ketoconazole has proven to be effective in the treatment of FMPP due to its ability to inhibit adrenal and gonadal steroidogenesis. However, there are safety concerns with ketoconazole which include liver toxicity and adrenal insufficiency and one case of liver failure (53) has been reported.

- Therefore, the most frequent approach currently involves the combination of an anti-androgen and an AI. The use of AI in the treatment of PPP stems from a recognition of the role of estrogen in epiphyseal fusion in boys and girls. A prospective study started in the 1990's utilized spironolactone and testolactone, which was eventually replaced with anastrozole. Final AH in treated patients significantly exceeded predicted AH at treatment start (173.8 ± 6.9 vs 164.9 ± 10.7 cm; $P < .001$) (54). Along the same lines, the combination of bicalutamide, a potent

selective androgen receptor inhibitor and a third generation AI was first tried in 2 patients and showed promising results laying the ground for additional studies (55). The BATT (Bicalutamide and Anastrozole Treatment of Testotoxicosis) study is a multicenter international prospective trial involving 13 patients with FMPP treated with bicalutamide (12.5-100mg daily) and anastrozole (0.5-1mg daily) for 1 year. Rates of growth and bone maturation decreased, with the ratio of BA to chronological age significantly declining from 2.1 ± 0.6 at baseline to 1.0 ± 0.4 at 1 year. Gynecomastia and breast tenderness were common occurring in 42.9% and 12.5% respectively (56). No long term results have been published for this study as of yet. However, results from a case report of 2 boys receiving this combination therapy (including letrozole in 1 patient) for up to 5 years were promising (57). Given limited data on the use of letrozole in FMPP, it is difficult to assess its efficacy compared to anastrozole.

4-Gonadal and adrenal tumors

Gonadal and adrenal tumors are rare causes of PPP. As in other causes of PPP, the sequence of events in pubertal development is altered and the tempo of progression may be more rapid compared to CPP.

A. Gonadal tumors

Sex cord–stromal cell tumors and germ cell tumors (GCTs) are the two types of gonadal tumors that are commonly associated with endocrine manifestations.

1-Sex cord-stromal tumors

Juvenile granulosa cell tumors (JGCT) are the most common sex cord-stromal cell tumors in the pediatric population (58). PPP is seen in up to 70% of JGCT (59). Affected children may manifest signs of androgen and/ or estrogen exposure. JGCT can secrete inhibin and mullerian inhibitory substance both of which can be used as tumor markers. These tumors have a favorable prognosis and unilateral salpingo-oophorectomy is considered curative.

Leydig cell tumors (LCT) are the most common hormone-producing tumors of the testes, and very rarely occur in the ovaries (60). Prepubertal boys present with signs of virilization and gynecomastia may occasionally be present due to estrogen production by the tumor or aromatization of testosterone to estrogen (61). Physical exam reveals asymmetric testes. Laboratory findings consist of elevated testosterone and suppressed gonadotropins. LCTs are typically benign in children and orchiectomy is considered curative (62).

Leydig and Sertoli cell tumors occur frequently in patients with Peutz-Jeghers syndrome, in whom signs of PPP may be the presenting manifestations (63, 64).

2-Germ cell tumors

GCTs are the most common ovarian tumors in children but are extremely rare in the testes. They include dysgerminomas, teratomas, and embryonal carcinomas. GCTs cause PPP via secretion of hCG which acts at the LH receptor in gonadal tissue to stimulate sex steroid production.

It is important to note that GCTs occur more commonly outside of the gonads, and PPP may be the only manifestation in this setting.

Extra-gonadal GCTs occur more commonly in patients with Klinefelter syndrome, particularly in the mediastinum (65).

An elevated serum β-HCG and/or α-fetoprotein level is characteristic of GCTs. However, these levels may be normal in CNS GCTs, and may only be elevated in CSF. Additionally, these tumors may be small and difficult to localize, posing additional challenges to making a diagnosis. Once treatment is started, serum testosterone level can be used as a tumor marker.

B. Adrenal tumors

Adrenocortical tumors (ACT) are rare causes of PPP and account for less than 1% of all childhood malignancies. The majority of these tumors occur in children younger than 4 years of age. ACTs have a strong genetic basis and have been described in association with several genetic syndromes, such as Li-Fraumeni syndrome, congenital hemihypertrophy, Beckwith-Wiedemann syndrome (BWS), MEN1, and Carney complex. Germline mutations of the *p53* gene, a tumor suppressor gene, were later identified in these conditions, as well as in children with sporadic ACT (66, 67). The association of BWS and ACT has unraveled additional genetic etiologies. The overexpression of IGF2 and inactivation of the *p57KIP2* tumor suppressor gene resulting from genetic abnormalities at the 11p15 locus are implicated in the development of ACT. Mutations in additional tumor suppressor genes such as *menin* in MEN1, and *PRKAR1A* in Carney complex have also been described in association with ACT. Importantly, PPP is not specific to any of the mutations

Histologically, ACTs consist of 2 subtypes; adenomas and carcinomas. Carcinomas are more common in children. Macroscopically, adenomas tend to be relatively small and well demarcated, whereas carcinomas tend to be large, lobulated and friable. Microscopic features such increased mitotic index, nuclear atypia and cellular pleiomorphism are associated with malignancy (68).

Diagnosis

The majority of ACT in children are functional and may autonomously oversecrete one or more of the 3 major classes of corticosteroids and often secrete a mixture of these. The most common clinical manifestations are signs of virilization resulting from excessive androgen production. Based on a registry of 254 children, signs of virilization were present either alone or in association with signs of glucocorticoid excess in 84% of patients (69). Signs of glucocorticoid excess include rapid weight gain, round face, facial plethora, striae, hypertension, hirsutism and glucose intolerance.

DHEA and DHEAS are the major androgens produced and can be used as tumor markers. Lab evaluation should also include testosterone as well as testing for cortisol excess if cushingoid features are present. Mineralocorticoid excess is rare and testing should be reserved for patients with suspicious clinical features.

Treatment

Complete surgical resection is the cornerstone of successful treatment, and results in an excellent prognosis whereas patients with unresectable disease have a dismal outcome (70). Once the tumor is resected, sex hormone levels rapidly decrease leading to regression of secondary signs of puberty. However, prolonged exposure to sex steroids can lead to activation of the HPG axis and CPP necessitating treatment with a GnRHa.

Conclusion

PPP is a heterogenous condition resulting from excess sex steroid production from gonadal or extra gonadal sources, independent of gonadotropin stimulation. The most common condition associated with PPP is CAH, which is usually due to 21 OHase deficiency resulting in excess androgen production.

While there is no standardized treatment for PPP in MAS, benefit may be obtained from letrozole or tamoxifen. Sex steroid producing ovarian tumors are rare, with JGCT being the most common. In boys, gonadal causes include FMPP and gonadal tumors, most commonly LCTs. Combination therapy with an anti-androgen and AI improves signs of virilization, and decreases rates of growth and skeletal maturation in boys with FMPP.

Practice Points:

- Steroid treatment for children with CAH should be optimized to preserve height potential and prevent long term effect of hyperand
- The decision to treat PPP in girls with MAS should be individualized based on frequency of menses and effect on skeletal matura options.
- Boys with FMPP should receive combination therapy with a 3rd generation AI and an anti-androgen. Similar treatment regimen ca
- PPP associated with gonadal or extra gonadal tumors typically resolves with treatment of primary tumor.
- CPP can develop in children with various forms of PPP, especially in those with advanced BA, and additional testing and treatme

Research Agenda:

- Studies to investigate the optimal steroid regimen for CAH are needed.
- Trials to determine long term safety of AIs in the management of PPP are necessary.
- The effects of combination therapy with 3rd generation AI and the selective antiandrogen bicalutamide on AH in children with FMP

Figure 1

Simplified representation of adrenal steroid biosynthesis. Dotted arrows represent reactions that occur primarily in the gonads.

3βHSD: 3β Hydroxysteroid dehydrogenase/isomerase

StAR: steroidogenic acute regulatory protein, involved in the transfer of cholesterol from outer to the inner mitochondrial membrane where desmolase, a side chain cleavage enzyme, is located.

Figure 2

Severely virilized external genitalia in a 46, XX newborn with 21 OHse deficiency

Figure 3

Classic appearance of café-au-lait macules in a boy with MAS

Table 1

Summary of the various pharmacological agents studied in girls with MAS and PPP

GV: growth velocity, BA: bone age, AI: aromatase inhibitor, FAH: final adult height

Phamacological agent	**Action**	**Number of patients (Study reference)**	**Duration of treatment**	**Efficacy**	**Adverse effects**

Cyproterone acetate	antiandrogen	Case reports (71, 72)		Decreased estradiol level No change in FAH	Glucocorticoid effect in high doses
Medroxyprogesterone acetate	Progestin: inhibits gonadal steroidogenesis	6 (73)	6-16 months	Decreased vaginal bleeding Regression in breast development Continued rapid GV in half	
Ketoconazole	P450 cytochrome inhibitor: inhibits adrenal and gonadal steroidogenesis	2 (32)	12 months	Cessation of menses Regression of signs of puberty	Pruritis
Testolactone	1st generation AI	12 (35)	6 months-5 years	Less efficacious overtime Decreased BA advancement but no change in FAH	Mild GI upset Headaches Liver enzyme elevation Need for frequent dosing/compliance issues
Fadrazole	2nd generation AI	16 (34)	12-33 months	No changes in GV, rate of BA advancement or	Adrenal insufficiency Abdominal pain

				frequency of menses	Muscle weakness
Anastrozole	3rd generation AI	27 (36)	12 months	No changes in GV, rate of BA advancement or frequency of menses	None
Letrozole	3rd generation AI	9 (38)	1-3 years	Decreased vaginal bleeding Decreased GV and rate of BA advancement	Increased ovarian volume and cyst size 1 child with hemorrhagic cyst and ovarian torsion GI Symptoms
Letrozole		28 (37)	6 months-10 years	Decreased rate of BA advancement Improved FAH	None
Tamoxifen	Estrogen receptor modulator	25 (38, 39)	12 months	Decreased GV, and rate of BA advancement Decreased frequency of menses	Increased ovarian and uterine volumes
Tamoxifen		8 (40)	3-8 years	Decreased frequency of menses Improved FAH	None
Fulvestrant	Pure estrogen	30	12 months	Decreased vaginal	None

	receptor antagonist	(41)		bleeding Decreased BA advancement	

Table 2

Summary of the various pharmacological agents studied in FMPP

GV: growth velocity, BA: bone age, AI: aromatase inhibitor, FAH: final adult height

Pharmacological agent	**Mode of action**	**Number of patients (Study reference)**	**Duration of treatment**	**Efficacy**	**Safety/ Limitations of the study**

Medroxyprogesterone	Progestin: inhibits gonadal steroidogenesis	2 (74)	5 years	Decreased testosterone Decreased GV	No FAH data
Cyproterone acetate	Anti-androgen	Case reports (48, 52)		Decreased testosterone Decreased GV and BA advancement No effect on FAH	None
Ketoconazole	P450 cytochrome inhibitor: inhibits adrenal and gonadal steroidogenesis	5 (52)	8 years	Decreased testosterone Decreased GV and BA advancement Limited effect on FAH	None
Ketoconazole		5 (75)	5-10 years	Decreased testosterone FAH similar to target height	Mild transaminitis Increased ACTH
Testolactone/spironolactone	First generation AI/ weak androgen receptor blocker	10 (76)	6 years	Decreased GV and BA advancement Improved predicted AH	No FAH data GI side effects Need for frequent dosing
Testolactone (later changed to 3rd generation AI)/spironolactone/GnRH agonist		28 (54)	7 years	Improved FAH	Mild GI side effects
Bicalutamide/anastrozole (BATT study)	Potent androgen receptor blocker/3rd generation AI	14 (56)	1 year	Decreased GV and BA advancement	Gynecomastia Breast tenderness short term data
Bicalutamide/anastrozole or letrozole	Letrozole: 3rd generation AI	2 (57)	4.5-5 years	Decreased GV and BA advancement Improved	none

				predicted AH	

Bibliography

1. Levine LS. Congenital adrenal hyperplasia. Pediatrics in review. 2000;21(5):159-70.
*2. Speiser PW, Arlt W, Auchus RJ, et al. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism. 2018;103(11):4043-88.
3. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. Lancet. 2005;365(9477):2125-36.
4. White PC, Grossberger D, Onufer BJ, et al. Two genes encoding steroid 21-hydroxylase are located near the genes encoding the fourth component of complement in man. Proceedings of the National Academy of Sciences of the United States of America. 1985;82(4):1089-93.
5. White PC, New MI, Dupont B. Structure of human steroid 21-hydroxylase genes. Proceedings of the National Academy of Sciences of the United States of America. 1986;83(14):5111-5.
6. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocrine reviews. 2000;21(3):245-91.
*7. Eugster EA, Dimeglio LA, Wright JC, et al. Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. The Journal of pediatrics. 2001;138(1):26-32.
8. Pescovitz OH, Comite F, Cassorla F, et al. True precocious puberty complicating congenital adrenal hyperplasia: treatment with a luteinizing hormone-releasing hormone analog. The Journal of clinical endocrinology and metabolism. 1984;58(5):857-61.
9. Azziz R, Woods KS, Reyna R, et al. The prevalence and features of the polycystic ovary syndrome in an unselected population. The Journal of clinical endocrinology and metabolism. 2004;89(6):2745-9.

10. Chrousos GP, Loriaux DL, Mann DL, Cutler GB, Jr. Late-onset 21-hydroxylase deficiency mimicking idiopathic hirsutism or polycystic ovarian disease. Annals of internal medicine. 1982;96(2):143-8.
*11. Lekarev O, Lin-Su K, Vogiatzi MG. Infertility and Reproductive Function in Patients with Congenital Adrenal Hyperplasia: Pathophysiology, Advances in Management, and Recent Outcomes. Endocrinology and metabolism clinics of North America. 2015;44(4):705-22.
12. Falhammar H, Nystrom HF, Ekstrom U, et al. Fertility, sexuality and testicular adrenal rest tumors in adult males with congenital adrenal hyperplasia. European journal of endocrinology. 2012;166(3):441-9.
13. Chaudhari M, Johnson EK, DaJusta D, Nahata L. Testicular adrenal rest tumor screening and fertility counseling among males with congenital adrenal hyperplasia. Journal of pediatric urology. 2018;14(2):155 e1- e6.
14. Smeets EE, Span PN, van Herwaarden AE, et al. Molecular characterization of testicular adrenal rest tumors in congenital adrenal hyperplasia: lesions with both adrenocortical and Leydig cell features. The Journal of clinical endocrinology and metabolism. 2015;100(3):E524-30.
15. Levine LS, S.A O. Congenital Adrenal hyperplasia. Pescovitz OH, Walvoord E, editors. New Jersey: Humana Press; 2007.
16. Nebesio TD, Renbarger JL, Nabhan ZM, et al. Differential effects of hydrocortisone, prednisone, and dexamethasone on hormonal and pharmacokinetic profiles: a pilot study in children with congenital adrenal hyperplasia. International journal of pediatric endocrinology. 2016;2016:17.
17. Leslie JA, Cain MP, Rink RC. Feminizing genital reconstruction in congenital adrenal hyperplasia. Indian journal of urology : IJU : journal of the Urological Society of India. 2009;25(1):17-26.
18. Sturm RM, Durbin-Johnson B, Kurzrock EA. Congenital adrenal hyperplasia: current surgical management at academic medical centers in the United States. The Journal of urology. 2015;193(5 Suppl):1796-801.
19. Berenbaum SA, Bailey JM. Effects on gender identity of prenatal androgens and genital appearance: evidence from girls with congenital adrenal hyperplasia. The Journal of clinical endocrinology and metabolism. 2003;88(3):1102-6.
20. Dacou-Voutetakis C, Karidis N. Congenital adrenal hyperplasia complicated by central precocious puberty: treatment with LHRH-agonist analogue. Annals of the New York Academy of Sciences. 1993;687:250-4.
21. Guven A, Nurcan Cebeci A, Hancili S. Gonadotropin releasing hormone analog treatment in children with congenital adrenal hyperplasia complicated by central precocious puberty. Hormones. 2015;14(2):265-71.
22. Lin-Su K, Vogiatzi MG, Marshall I, et al. Treatment with growth hormone and luteinizing hormone releasing hormone analog improves final adult height in children with congenital adrenal hyperplasia. The Journal of clinical endocrinology and metabolism. 2005;90(6):3318-25.
23. Lin-Su K, Harbison MD, Lekarev O, et al. Final adult height in children with congenital adrenal hyperplasia treated with growth hormone. The Journal of clinical endocrinology and metabolism. 2011;96(6):1710-7.
24. Weinstein LS, Shenker A, Gejman PV, et al. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. The New England journal of medicine. 1991;325(24):1688-95.
*25. Shenker A, Weinstein LS, Moran A, et al. Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of stimulatory G protein GS. The Journal of pediatrics. 1993;123(4):509-18.
26. Haddad N, Eugster E. An update on the treatment of precocious puberty in McCune-Albright syndrome and testotoxicosis. Journal of pediatric endocrinology & metabolism : JPEM. 2007;20(6):653-61.
27. Casey R; Boyce A EA, et al. Implications for the Future of Pediatric and Adolescent Girls With McCune-Albright Syndrome: Long Term Obstetrical and Gynecologic Outcomes2015; Oral Abstracts / J Pediatr Adolesc Gynecol 28 [e32 p.].
28. Boyce AM, Chong WH, Shawker TH, et al. Characterization and management of testicular pathology in McCune-Albright syndrome. The Journal of clinical endocrinology and metabolism. 2012;97(9):E1782-90.

29. Coutant R, Lumbroso S, Rey R, et al. Macroorchidism due to autonomous hyperfunction of Sertoli cells and G(s)alpha gene mutation: an unusual expression of McCune-Albright syndrome in a prepubertal boy. The Journal of clinical endocrinology and metabolism. 2001;86(4):1778-81.
30. Wasniewska M, De Luca F, Bertelloni S, et al. Testicular microlithiasis: an unreported feature of McCune-Albright syndrome in males. The Journal of pediatrics. 2004;145(5):670-2.
31. Nabhan ZM, West KW, Eugster EA. Oophorectomy in McCune-Albright syndrome: a case of mistaken identity. Journal of pediatric surgery. 2007;42(9):1578-83.
32. Syed FA, Chalew SA. Ketoconazole treatment of gonadotropin independent precocious puberty in girls with McCune-Albright syndrome: a preliminary report. Journal of pediatric endocrinology & metabolism : JPEM. 1999;12(1):81-3.
33. Vermeer LM, Isringhausen CD, Ogilvie BW, Buckley DB. Evaluation of Ketoconazole and Its Alternative Clinical CYP3A4/5 Inhibitors as Inhibitors of Drug Transporters: The In Vitro Effects of Ketoconazole, Ritonavir, Clarithromycin, and Itraconazole on 13 Clinically-Relevant Drug Transporters. Drug metabolism and disposition: the biological fate of chemicals. 2016;44(3):453-9.
34. Nunez SB, Calis K, Cutler GB, Jr., et al. Lack of efficacy of fadrozole in treating precocious puberty in girls with the McCune-Albright syndrome. The Journal of clinical endocrinology and metabolism. 2003;88(12):5730-3.
35. Feuillan PP, Jones J, Cutler GB, Jr. Long-term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. The Journal of clinical endocrinology and metabolism. 1993;77(3):647-51.
36. Mieszczak J, Lowe ES, Plourde P, Eugster EA. The aromatase inhibitor anastrozole is ineffective in the treatment of precocious puberty in girls with McCune-Albright syndrome. The Journal of clinical endocrinology and metabolism. 2008;93(7):2751-4.
*37. Estrada A, Boyce AM, Brillante BA, et al. Long-term outcomes of letrozole treatment for precocious puberty in girls with McCune-Albright syndrome. European journal of endocrinology. 2016;175(5):477-83.
38. Feuillan P, Calis K, Hill S, et al. Letrozole treatment of precocious puberty in girls with the McCune-Albright syndrome: a pilot study. The Journal of clinical endocrinology and metabolism. 2007;92(6):2100-6.
39. Eugster EA, Rubin SD, Reiter EO, et al. Tamoxifen treatment for precocious puberty in McCune-Albright syndrome: a multicenter trial. The Journal of pediatrics. 2003;143(1):60-6.
*40. de GBPC, Kuperman H, Cabral de Menezes-Filho H, et al. Tamoxifen Improves Final Height Prediction in Girls with McCune-Albright Syndrome: A Long Follow-Up. Hormone research in paediatrics. 2015;84(3):184-9.
41. Sims EK, Garnett S, Guzman F, et al. Fulvestrant treatment of precocious puberty in girls with McCune-Albright syndrome. International journal of pediatric endocrinology. 2012;2012(1):26.
42. Tessaris D, Matarazzo P, Mussa A, et al. Combined treatment with bicalutamide and anastrozole in a young boy with peripheral precocious puberty due to McCune-Albright Syndrome. Endocrine journal. 2012;59(2):111-7.
43. Rousseau-Merck MF, Misrahi M, Atger M, et al. Localization of the human luteinizing hormone/choriogonadotropin receptor gene (LHCGR) to chromosome 2p21. Cytogenetics and cell genetics. 1990;54(1-2):77-9.
*44. Shenker A, Laue L, Kosugi S, et al. A constitutively activating mutation of the luteinizing hormone receptor in familial male precocious puberty. Nature. 1993;365(6447):652-4.
45. Nabhan ZM, Eugster E. Testotoxicosis with an episodic course: an unusual case within a series. Endocrine Practice [Internet]. 2018.
46. Holland FJ, Kirsch SE, Selby R. Gonadotropin-independent precocious puberty ("testotoxicosis"): influence of maturational status on response to ketoconazole. The Journal of clinical endocrinology and metabolism. 1987;64(2):328-33.
47. Reiter EO, Brown RS, Longcope C, Beitins IZ. Male-limited familial precocious puberty in three generations. Apparent Leydig-cell autonomy and elevated glycoprotein hormone alpha subunit. The New England journal of medicine. 1984;311(8):515-9.
48. Bertelloni S, Baroncelli GI, Lala R, et al. Long-term outcome of male-limited gonadotropin-independent precocious puberty. Hormone research. 1997;48(5):235-9.

49. Egli CA, Rosenthal SM, Grumbach MM, et al. Pituitary gonadotropin-independent male-limited autosomal dominant sexual precocity in nine generations: familial testotoxicosis. The Journal of pediatrics. 1985;106(1):33-40.
50. Martin MM, Wu SM, Martin AL, et al. Testicular seminoma in a patient with a constitutively activating mutation of the luteinizing hormone/chorionic gonadotropin receptor. European journal of endocrinology. 1998;139(1):101-6.
51. Leschek EW, Chan WY, Diamond DA, et al. Nodular Leydig cell hyperplasia in a boy with familial male-limited precocious puberty. The Journal of pediatrics. 2001;138(6):949-51.
52. Almeida MQ, Brito VN, Lins TS, et al. Long-term treatment of familial male-limited precocious puberty (testotoxicosis) with cyproterone acetate or ketoconazole. Clinical endocrinology. 2008;69(1):93-8.
53. Babovic-Vuksanovic D, Donaldson MD, Gibson NA, Wallace AM. Hazards of ketoconazole therapy in testotoxicosis. Acta paediatrica. 1994;83(9):994-7.
*54. Leschek EW, Flor AC, Bryant JC, et al. Effect of Antiandrogen, Aromatase Inhibitor, and Gonadotropin-releasing Hormone Analog on Adult Height in Familial Male Precocious Puberty. The Journal of pediatrics. 2017;190:229-35.
55. Kreher NC, Pescovitz OH, Delameter P, et al. Treatment of familial male-limited precocious puberty with bicalutamide and anastrozole. The Journal of pediatrics. 2006;149(3):416-20.
*56. Reiter EO, Mauras N, McCormick K, et al. Bicalutamide plus anastrozole for the treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis: a phase II, open-label pilot study (BATT). Journal of pediatric endocrinology & metabolism : JPEM. 2010;23(10):999-1009.
57. Lenz AM, Shulman D, Eugster EA, et al. Bicalutamide and third-generation aromatase inhibitors in testotoxicosis. Pediatrics. 2010;126(3):e728-33.
58. Schneider DT, Calaminus G, Harms D, Gobel U, German Maligne Keimzelltumoren Study G. Ovarian sex cord-stromal tumors in children and adolescents. The Journal of reproductive medicine. 2005;50(6):439-46.
59. Breen JL, Maxson WS. Ovarian tumors in children and adolescents. Clinical obstetrics and gynecology. 1977;20(3):607-23.
60. Olivier P, Simoneau-Roy J, Francoeur D, et al. Leydig cell tumors in children: contrasting clinical, hormonal, anatomical, and molecular characteristics in boys and girls. The Journal of pediatrics. 2012;161(6):1147-52.
61. Johnstone G. Prepubertal gynaecomastia in association with an interstitial-cell tumour of the testis. British journal of urology. 1967;39(2):211-20.
62. Cheville JC, Sebo TJ, Lager DJ, et al. Leydig cell tumor of the testis: a clinicopathologic, DNA content, and MIB-1 comparison of nonmetastasizing and metastasizing tumors. The American journal of surgical pathology. 1998;22(11):1361-7.
63. Young S, Gooneratne S, Straus FH, et al. Feminizing Sertoli cell tumors in boys with Peutz-Jeghers syndrome. The American journal of surgical pathology. 1995;19(1):50-8.
64. Hemminki A. The molecular basis and clinical aspects of Peutz-Jeghers syndrome. Cellular and molecular life sciences : CMLS. 1999;55(5):735-50.
65. Aguirre D, Nieto K, Lazos M, et al. Extragonadal germ cell tumors are often associated with Klinefelter syndrome. Human pathology. 2006;37(4):477-80.
66. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science. 1990;250(4985):1233-8.
67. Ribeiro RC, Sandrini F, Figueiredo B, et al. An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(16):9330-5.
68. Medeiros LJ, Weiss LM. New developments in the pathologic diagnosis of adrenal cortical neoplasms. A review. American journal of clinical pathology. 1992;97(1):73-83.
69. Michalkiewicz E, Sandrini R, Figueiredo B, et al. Clinical and outcome characteristics of children with adrenocortical tumors: a report from the International Pediatric Adrenocortical Tumor Registry. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2004;22(5):838-45.
70. Mayer SK, Oligny LL, Deal C, et al. Childhood adrenocortical tumors: case series and reevaluation of prognosis--a 24-year experience. Journal of pediatric surgery. 1997;32(6):911-5.

71. Carani C, Pacchioni C, Baldini A, Zini D. Effects of cyproterone acetate, LHRH agonist and ovarian surgery in McCune-Albright syndrome with precocious puberty and galactorrhea. Journal of endocrinological investigation. 1988;11(6):419-23.
72. Sorgo W, Kiraly E, Homoki J, et al. The effects of cyproterone acetate on statural growth in children with precocious puberty. Acta endocrinologica. 1987;115(1):44-56.
73. Rao S, Colaco MP, Desai MP. McCune Albright Syndrome (MCAS): a case series. Indian pediatrics. 2003;40(1):29-35.
74. Rosenthal SM, Grumbach MM, Kaplan SL. Gonadotropin-independent familial sexual precocity with premature Leydig and germinal cell maturation (familial testotoxicosis): effects of a potent luteinizing hormone-releasing factor agonist and medroxyprogesterone acetate therapy in four cases. The Journal of clinical endocrinology and metabolism. 1983;57(3):571-9.
*75. Soriano-Guillen L, Lahlou N, Chauvet G, et al. Adult height after ketoconazole treatment in patients with familial male-limited precocious puberty. The Journal of clinical endocrinology and metabolism. 2005;90(1):147-51.
76. Leschek EW, Jones J, Barnes KM, et al. Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. The Journal of clinical endocrinology and metabolism. 1999;84(1):175-8.