



Published in final edited form as:

*Pediatr Endocrinol Rev.* 2017 December ; 15(2): 136–141.

## Treatment of Girls and Boys with McCune-Albright Syndrome with Precocious Puberty – Update 2017

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### Abstract

The most common endocrinopathy associated with McCune-Albright Syndrome (MAS) is peripheral precocious puberty (PP) which occurs far more often in girls than in boys. We will discuss the latest advancements in the treatment of precocious puberty in MAS that have been achieved during the past 10 years. However, due to the rarity of the condition and the heterogeneity of the disease, research in this field is limited particularly in regards to treatment in boys. In girls, a period of watchful waiting is recommended prior to initiating therapy due to extreme variability in the clinical course. This article will review in detail current pharmacologic treatment in girls, which typically consists of either inhibiting estrogen production or blocking estrogen action at the level of the end-organ. The two treatments with the most evidence at this time are Tamoxifen (which is an estrogen receptor modulator) and Letrozole (which is a 3rd generation aromatase inhibitor). This article will also review the current treatment strategies in boys which typically include using an androgen receptor blocker and an aromatase inhibitor. Due to the rarity of the condition, large multicenter collaborative studies are needed to further investigate efficacy and safety with the goal of establishing the gold standard for treatment of PP in children with MAS.

### Keywords

McCune-Albright Syndrome; Precocious Puberty; Tamoxifen; Letrozole; Bicalutamide

### Introduction

McCune-Albright syndrome (MAS) is a rare genetic disorder with a prevalence of between 1:100,000 and 1:1,000,000 (1). It is caused by an activating post-zygotic somatic mutation in the *GNAS1* gene which leads to increased GS $\alpha$  protein signaling. This results in continuous activation of adenylyl cyclase leading to increased cAMP and ligand independent amplification of the downstream effects (1,2). MAS is classically characterized by the triad of fibrous dysplasia of bone (classic x-ray finding is of a hazy, radiolucent, “ground glass appearance”), café-au-lait skin pigmentation, and peripheral precocious puberty (PP) (1,3,4).

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### Disclosure

The authors report no conflicts of interest in this work.

However, there are other associated endocrinopathies including hyperthyroidism, Cushing syndrome, GH excess and renal phosphate wasting (2) in addition to rare cases of widespread multi-systemic involvement (5). This review will provide an update of the treatment of PP in children with MAS with a focus on knowledge that has accumulated during the last ~10 years.

## Precocious Puberty in Girls

Girls with MAS are much more likely to develop PP than boys. Affected girls have autonomously functioning unilateral ovarian cysts which lead to significantly high serum estradiol concentrations with suppressed gonadotropins (2,6). In patients with classic MAS, a single suppressed LH may be sufficient for the diagnosis. Girls with PP typically present in early childhood with painless vaginal bleeding which may be profuse, and minimal if any breast development (it may have resolved by the time the patient is seen). PP is typically the first manifestation of the disorder, and in atypical cases it may be the only feature (2,6). Therefore, it is important to evaluate patients who present with an isolated autonomous ovarian cyst for MAS (7). If the evaluation is consistent with MAS, the patient should have a bone scan to evaluate for fibrous dysplasia as well as laboratory tests to screen for other endocrinopathies. Genetic testing for a *GNAS1* mutation is available. However, due to the mosaic nature of the mutation, it may be falsely negative in peripheral blood. The likelihood of finding a mutation improves substantially if affected tissue is analyzed (2). There is a high variability in the clinical course of girls with MAS and PP. While some girls have repeated episodes of estrogen exposure leading to frequent vaginal bleeding, advanced bone age and growth acceleration, others have extended periods of disease inactivity (2). Thus, an initial period of observation prior to pharmacologic intervention is recommended following a new diagnosis of MAS and PP. Interestingly, periodic autonomously functioning ovarian cysts continue to occur in the post-pubertal years and may result in irregular bleeding and prolonged hyperestrogenism in adolescent and adult women with MAS (8).

## Treatment in Girls

Various therapies have been used to treat PP in affected girls. The goal of treatment is to decrease estrogen exposure with the objective of preventing vaginal bleeding, halting pubertal progression and improving adult height. GnRH analogs as a primary intervention are not successful due to the fact that the HPG axis is not involved in the sex steroid production in peripheral PP. However, over time many patients develop secondary central PP at which point the addition of a GnRH analog is beneficial (9).

In the past, cyproterone acetate and medroxyprogesterone demonstrated short term efficacy in controlling vaginal bleeding and breast development. In contrast, neither agent has been shown to influence growth rates or adult height, and are therefore considered inadequate for the treatment of PP in girls with MAS (2,10,11). The current therapeutic armamentarium is comprised of medications that either inhibit estrogen biosynthesis or block its effects at the level of the end organ. It should be noted that periodic episodes of autonomous ovarian function continue regardless of treatment status since anti-estrogen therapy has no impact on the underlying pathophysiology of the disease. The extreme rarity of the condition and the

pleomorphic nature of its clinical manifestations represent important obstacles to rigorous investigation of therapeutic strategies for PP. Regardless, important insights pertaining to a number of medications have been gleaned from case reports, non-randomized prospective studies (in which girls function as their own controls) and limited long-term retrospective follow-up. Available data regarding each of these is discussed in the following section while studies published since 2007 are summarized in Table 1.

*Ketoconazole* is a non-specific inhibitor of cytochrome p450 enzymes and so can block both adrenal and gonadal steroidogenesis (12). It was used successfully in 2 girls with MAS in whom it caused cessation of menstrual cycles, regression of secondary sexual characteristics, decreased estradiol levels and attenuated bone age advancement (12). However, there is concern regarding long term safety with ketoconazole due to the risk of adrenal insufficiency and hepatotoxicity (13). Therefore, no prospective studies involving ketoconazole for the treatment of PP in girls with MAS have been pursued (12).

Aromatase inhibitors inhibit aromatase which is the enzyme that converts androgens to estrogens (14). This class of medications is used in both girls and boys with forms of peripheral PP. *Testolactone* (which is a 1st generation aromatase inhibitor) was initially attempted and found to be minimally successful. One study followed 12 girls treated for 0.5–5 years, 7 of whom received testolactone for at least 3 years. Although reductions in serum estradiol levels and frequency of vaginal bleeding were noted, mean predicted adult heights were not significantly improved after treatment. Positive results were most evident in the first year, consistent with an escape phenomenon of the medication (15). Additionally, testolactone requires being dosed 4 times a day, and so it is not routinely used (16).

*Fadrazole* is a 2nd generation aromatase inhibitor, although it is not specific to aromatase, as previous studies in adults have shown a blunting of cortisol and aldosterone (17). One study involved 16 girls who were treated with fadrazole and did not find it to be effective. In the group as a whole, there was no significant decrease in skeletal maturation, mean growth rate SDS or predicted adult height. Likewise, there was no significant decrease in mean estradiol levels or mean ovarian volumes. While vaginal bleeding decreased initially, this was not sustained. There was also a dose dependent decrease in cortisol and an increase in renin activity level. Three patients were found to have biochemical evidence of adrenal insufficiency and were started on hydrocortisone replacement. In 2 girls the adrenal axis returned to normal after discontinuation of the medication whereas the 3rd continued to have mild adrenal insufficiency. Due to lack of effectiveness for the group as a whole and the concern for side effects, newer aromatase inhibitors with greater potency and specificity were studied (17).

*Anastrozole* is a 3<sup>rd</sup> generation aromatase inhibitor. A prospective, international, multi-institutional trial was conducted in 28 girls for one year with disappointing results. The study found no difference in bone age advancement, frequency of vaginal bleeding, or mean ovarian or uterine volumes with treatment. While growth velocity z-scores did decrease, this was not statistically significant. Although anastrozole appeared safe in the study, its lack of efficacy renders it a poor choice for the treatment of PP in girls with MAS (18).

*Letrozole* is a potent long-acting 3rd generation aromatase inhibitor (19). An initial pilot study in 9 girls with MAS who were treated for up to 36 months was conducted. The study found a significant decrease in growth velocity SDS ( $p= 0.01$ ) and bone age maturation ( $p= 0.004$ ). Mean serum estradiol and ovarian volumes fell at 6 months but usually increased by 12–24 months, although these changes did not reach statistical significance. Six of the 9 girls stopped having vaginal bleeding and 3 others had a reduction in the frequency of bleeds. The therapy was well tolerated, although 1 patient developed a large ovarian cyst with torsion that required surgical intervention, representing a potential safety signal related to the use of letrozole in this clinical population (19).

Results from a single-center retrospective cohort study of 28 girls including the 9 from the initial pilot study who received at least 6 months of letrozole treatment have been published. Rates of bone age maturation and mean growth velocity z-scores significantly decreased and there was a significant increase in predicted adult height z-scores (20). In the 4 patients who had reached adult height, the mean z-score was statistically increased in comparison with untreated historical controls. Vaginal bleeding episodes and estradiol levels decreased, and there was no change in uterine or ovarian volumes. No adverse events were reported during the study period, including no further incidents of ovarian torsion. In conclusion this study found that unlike other aromatase inhibitors, letrozole appears to be an effective treatment for MAS associated PP that is also likely safe (20).

Another class of medications that has been used in girls with MAS-associated PP are estrogen receptor modulators such as *tamoxifen*. A multicenter prospective study was performed in 28 girls who were treated for 1 year. Episodes of vaginal bleeding decreased and a significant reduction in growth velocity SDS and rates of bone maturation was observed. No adverse effects were reported although uterine volumes increased during treatment with tamoxifen. Thus, periodic pelvic ultrasounds are recommended in girls treated with this modality due to theoretical concerns about tamoxifen associated stromal tumors although none have been reported in the setting of MAS to date (21).

A retrospective follow-up study in 8 patients treated with tamoxifen for 3–8 years and monitored for a mean period of 8.3 years (range 3–16 years) was reported. All had cessation of vaginal bleeding and stabilization of bone maturation. A significant difference between the predicted adult height (PAH) at the beginning of treatment and at the end of treatment was also observed (22). However, final heights in the 4 patients who had completed growth was less than predicted, although only 1 had an adult height below 2 standard deviations. Tamoxifen was well tolerated, with no adverse effects noted, including no changes in bone mineral density (BMD) or alterations in the uterine endometrium. In conclusion the results support a role for tamoxifen in treating PP and improving PAH in girls with MAS, albeit the effect on adult height may not be as robust in follow-up as initially predicted (22).

*Fulvestrant* is a pure estrogen receptor blocker that is administered via monthly intramuscular injection. An international, prospective study enrolled 30 girls who were treated for 1 year. Median annual vaginal bleeding days decreased from 12.0 to 1.0 with a median change in frequency of 3.6 days ( $p=0.0146$ ) (23). The ratio of bone age to chronological age also significantly decreased. There was no statistically significant change

in mean growth velocity z-scores and no change in PAH. There was no significant change in uterine size. The most common adverse reaction was at the site of injection. The authors concluded that longer treatment with fulvestrant might have led to improved PAH, as there was a progressive decrease in bone age advancement throughout the study (23).

*Surgery* (including cystectomy or oophorectomy) is not recommended due to the cysts likely recurring and concerns about a negative impact on fertility (2). Unfortunately, unnecessary oophorectomy has been reported due to a failure to include MAS in the differential diagnosis of a prepubertal girl presenting with sudden onset of vaginal bleeding and an apparent ovarian mass (24).

## Precocious Puberty in Boys

PP is uncommon in boys with MAS. It is caused by Leydig cell hyperplasia and increased testosterone production which in turn leads to a premature increase in penile size and mild bilateral testicular enlargement (2). Labs demonstrate elevated serum testosterone and suppressed gonadotropins.

Cases in which a Sertoli cell only *GNAS1* activating mutation is present have been reported and result in unilateral or bilateral macroorchidism without PP (25). A prospective cohort study with 54 subjects was undertaken to evaluate the spectrum of testicular pathology in boys with MAS. The authors found that 44% of the subjects with a recorded testicular volume had asymptomatic macroorchidism which was usually bilateral. Interestingly 81% of the subjects had testicular abnormalities on ultrasound, the most common of which were hyperechoic lesions, but hypoechoic lesions, microlithiasis, heterogeneity, and focal calcifications were also seen (26). Twenty-one percent of this cohort presented with PP. The investigators concluded that even though the incidence of PP is low in boys with MAS, the incidence of gonadal involvement is the same between the genders (26). In boys who had an indication for surgical excision the predominant finding was Leydig cell hyperplasia (LCH) which carries a low risk for malignant transformation. Of note however, is that one subject developed bilateral germ cell tumors. Based on these findings, the authors recommend following testicular lesions conservatively through close observation and serial imaging with the goal of testicular preservation (26).

## Treatment in Boys

There are limited data regarding treatment of PP in boys with MAS. The most common approach is to use an androgen receptor blocker and an aromatase inhibitor as is the case in other forms of peripheral PP in boys (2,25). The goal of treatment is to slow virilization with the ultimate aim of improving final height. Given the scarcity of affected boys, available information is primarily derived from isolated case reports.

Combination therapy was successful in a single case involving a boy with MAS who was treated with the antiandrogen bicalutamide and anastrozole. He was initially diagnosed with PP at 4.6 years old. He was treated with bicalutamide 25mg/day and anastrozole 1mg/day for 49 months (3). His growth velocity and penile length decreased, and there were no signs of progression of secondary sexual characteristics or gynecomastia. There was a rapid

reduction in masturbatory behaviors and frequency of erections. Bone age was equal to chronological age at the end of the follow-up period. The therapy was well tolerated, LFTs remained normal, and there was no modification of BMD (3).

Another case report described a boy with atypical MAS who was treated with the combination of ketoconazole, cyproterone acetate and leuprolide. He was 4.6 years when he presented with unilateral macroorchidism with no signs of PP. Initially he was followed over time. He then developed PP and at 6.6 years he was started on ketoconazole (400mg/daily in 2 divided doses) and cyproterone acetate (50mg/daily). During the first 12 months the size of his right testicle decreased, there was a decrease in testosterone and a significant deceleration of growth velocity and rate of skeletal maturation (27). However, during the 2nd year of treatment the changes were not as pronounced, likely due to the fact that he had entered central puberty. He was then started on leuprolide. During the next 4.2 years a decline in growth velocity and bone maturation were again noted. Therapy was stopped at 13 years and central puberty ensued. There were no reported side effects and no changes in transaminase levels. His adult height (188.5cm) exceeded his target height (181.2cm) and was close to the predicted height at the start of treatment (191.8cm) (27).

## Conclusion

In summary, important strides have been made in the treatment of PP in girls and boys with MAS since 2007. Particularly in view of information pertaining to long-term follow-up, both letrozole and tamoxifen have emerged as favorable options for first-line treatment in girls. Despite these advances, there remains a need for research in this condition, especially in boys. Due to the rarity of the disorder, collaborative, multicenter, prospective studies are essential in order to confirm efficacy and safety and establish a gold standard for treatment.

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**Table 1**  
Recent studies published (from 2008–present) for treating precocious puberty on girls with MAS

Author (ref #)	Year of Pub	Drug (Action)	N (completed therapy)	Study Design	Duration of Treatment	Efficacy	Safety Concerns
Mieszczak, J., <i>et al.</i> (18)	2008	Anastrozole (3 <sup>rd</sup> Generation Aromatase inhibitor)	28 (27)	Prospective, International, Multi-institutional, Open-label	12 months	No change in menses or BA advancement. GV z-scores decreased but not statistically significant	No significant adverse outcomes
Sims, EK., <i>et al.</i> (23)	2012	Fulvestrant (Pure Estrogen Receptor Blocker)	30 (29)	Prospective International, Multi-institutional, Open-label trial	12 months	Decreased menses*, decrease in BA advancement*. No statistically significant change in mean GV, no change in PAH	Generally well tolerated, most common event reported was reaction at the site (n=7), also reported vomiting (n=1), abdominal pain (n=1). No serious treatment-related adverse events
de, G.B.P.C., <i>et al.</i> (22)	2015	Tamoxifen (Selective Estrogen Receptor Modulator)	8	Retrospective	3–8 years	Stabilization of bone maturation*, cessation of menses, PAH increased* (however the 4 patients who reached FH were less than predicted)	No adverse events
Estrada, A., <i>et al.</i> (20)	2016	Letrozole (3 <sup>rd</sup> Generation Aromatase Inhibitor)	28	Retrospective, Cohort study, Single center	6 months to 10.9 years	Decrease in BA advancement*, decreased GV z-scores*, decreased menses*, PAH increased*	No adverse events. No additional cases of ovarian torsion, one noted in initial pilot study

\*  $P < 0.05$

BA: Bone Age

GV: Growth Velocity

PAH: Predicted Adult Height