

oxidoreductase (*POR*, OMIM 124015, chromosome 7q11.2), a flavoprotein that contributes electrons to all microsomal P450 enzymes. It does so by binding to NADPH through its flavin adenine dinucleotide (FAD) domain to which NADPH contributes 2 electrons; these electrons are then transferred to the flavin mononucleotide (FMN) domain of *POR* that, in turn, donates them to the target P450 enzyme. Mutations in *CYP17A1* that involve its binding to *POR* lead to decreased 17 α -hydroxylase activity. Accordingly, these investigators analyzed *POR* in 7 patients with combined deficiencies of 17 α - and 21-hydroxylase deficiency, some of whom had clinical and skeletal anomalies consistent with ABS. They found compound heterozygous or homozygous loss-of-function mutations in all patients including: 531T \Rightarrow G: Tyr178Asp; 731+1G \Rightarrow A: donor splice site intron 6; *859G \Rightarrow C: Ala287Pro; *1370G \Rightarrow A: Arg457His; 1475T \Rightarrow A: Val492Glu; *1706G \Rightarrow A: Cys569Tyr; 1822G \Rightarrow T: Val608Phe. The Ala287, Arg457, and Val492 mutations were in the FAD domain that binds NADPH and, predictably, changed steric conformation or charge leading to greatly reduced 17 α -hydroxylase and 17-20-lyase activities. The Cys569 and Val608 mutations were in the region that binds NADP⁺ and resulted in less loss of enzyme activity. Patients with ABS tended to have the more severe mutations in *POR*, while those with the less severe defects only had disordered steroidogenesis. In no patient studied was a mutation in *FGFR2* identified.

Fluck CE, Tajima T, Pandey AV, et al. Mutant P450 oxidoreductase causes disordered steroidogenesis with and without Antley-Bixler syndrome. *Nat Genet.* 2004;36:228-30.

Arlt W, Walker EA, Draper N, et al. Congenital adrenal hyperplasia caused by mutant P450 oxidoreductase and human androgen synthesis: analytical study. *Lancet.* 2004;363:2128-35.

Editor's Comment: *Pregnant women who are heterozygous carriers of a loss-of-function mutation in POR may manifest gestational hyperandrogenism (acne, hirsutism) possibly due to the effects of both fetal hyperandrogenemia and impaired endogenous steroidogenesis. This resembles the hyperandrogenism seen in patients with a luteoma of pregnancy or placental aromatase deficiency. Arlt et al suggest that in the fetus with loss of POR activity, an alternate pathway of androgen synthesis is pursued: 17 α -hydroxyprogesterone is converted to 5 α -pregnane-3, 17 α -diol-20-one and the latter to androsterone by sequential actions of 5 α -reductase type I, 3 α -hydroxysteroid dehydrogenase, and low levels of 17 α -hydroxylase. Since this pathway disappears in early infancy, virilization does not progress. These data suggest that ABS is genetically heterogeneous; one type is due to loss of FGFR2, and is not associated with genital malformation; the second type is due to loss of POR. POR is required for activity of both adrenal and hepatic microsomal P450 enzymes. Indeed, in infants of mothers treated with the antifungal agent fluconazole, that inhibits ergosterol synthesis by interfering with lanosterol 14 α -demethylase activity, skeletal deformities resembling those in neonates with ABS have been observed. The skeletal deformities observed in children with deficiency of POR may reflect an error in this pathway that affects skeletal embryogenesis.*

Allen W. Root, MD

Prevention of Progression from Pubarche to Polycystic Ovarian Syndrome

There is evidence that girls with low birth weight (LBW) and precocious pubarche (prior to 8 years of age) are at high risk of polycystic ovarian syndrome (PCOS) even if not obese. Ibáñez and colleagues performed a randomized early prevention study in 24 such girls 6 to 12 months post-menarche. In each, precocious pubarche was diagnosed by high serum androstenedione and/or DHEAS levels. To be included in the study, girls had to have a birth weight for gestational age <-1.5 SD, BMI $<26\%$, hyperinsulinemia on a 2-hour OGTT (peak serum insulin >150 μ U/mL or mean serum insulin >84 mU/L), and subclinical ovarian hyperandrogenism (17-HO progesterone response >160 ng/dL to GnRH agonist). They were randomized to receive either metformin 850 mg once daily or no treatment for 12 months. Serial clinical and biochemical measurements were made throughout the study.

There were no differences in any parameter between the treated and untreated groups at baseline. All subjects had increased androgen levels, abnormal lipid profiles, increased total body fat and reduced lean body mass. By 12 months, the treated group showed significant decreases in androgen levels, LDL cholesterol, and total body and truncal fat mass, and increases in HDL

cholesterol and lean body mass. In addition, insulin resistance was normalized. Most of these effects were seen between 3 and 6 months of treatment. The untreated group had significant worsening of each of these parameters. The authors conclude that the early post-menarchal years are an important period in the evolution of PCOS in girls with the predisposing clinical criteria. The authors also noted that the intervention was effective although limited to a once-daily medication without any other lifestyle change.

Ibáñez L, Ferrer A, Ong K, Amin R, Dunger D, de Zegher F. Insulin sensitization early after menarche prevents progression from precocious pubarche to polycystic ovary syndrome. *J Pediatr.* 2004;144:23-29.

Editor's Comment: *This is an important and well-designed study performed by a group of investigators with significant research experience in this area. Their suggested pathophysiologic schema for the development of PCOS consists of girls with LBW but normal catch-up growth who maintain reduced muscle mass and become insulin resistant. This predisposes them to central obesity and excessive fat mass despite appearing lean, as well as to PCOS. Ibáñez and colleagues also suggest that their*

data provided evidence that the endocrine-metabolic state is primary rather than secondary in this process. These are provocative conclusions and, if applicable to other patient populations, suggest an important role for insulin sensitizers, such as metformin, in the prevention of PCOS. Most pediatric endocrinologists are encountering more patients with PCOS. Therapy often includes metformin, an androgen-receptor blocker, and/or oral contraceptives,

but the results are rarely satisfactory. Clearly, there is a need to prevent the development of this syndrome. The etiology may not be the same in all cases, but close follow-up is merited in all girls born with LBW, as well as all girls presenting with premature pubarche. It is not unreasonable to suggest preventive therapy in some of these children.

William L. Clarke, MD

Improving Accuracy of Linear Growth Measurements

A survey study of pediatric and family primary care practices in 8 areas of the United States found that 70% employed inaccurate techniques for measuring children.¹ As follow-up, Lipman et al analyzed the effectiveness of an intervention aimed at improving the accuracy of linear growth measurements. From the 259 prior practice responders, 8 per geographic area were randomly recruited and divided into intervention and control arms of the trial of 55 practices (44 pediatric and 11 family practice). Practices cared for an average of 4000 children, and employed an average of 3.6 staff responsible for the measurements (21% RNs, 23% LPNs, 56% nurses' aides/medical assistants) with an average of 8.2 years experience. At baseline, correct overall measurement technique was demonstrated on 30% of measurements. Proper equipment was used in 58% of standing measured children and in 18% of recumbently measured children. The measurements differed by an average of 1.2 cm within the same child by study staff (differences ranged up to 12.1 cm). The intervention group received: a written pre-test of knowledge of growth measurement, a slide presentation and handouts on both proper measuring techniques and the physiology/pathophysiology of growth disorders, the installation of accurate measuring equipment and demonstration (plus return demonstration) on the correct measurement of height

and length, and a written post-test assessment. The control group received no intervention. Measurement techniques were re-evaluated after 3 and 6 months in both groups. Accurate measurement in the control group remained at 37% at 3 months and 34% at 6 months. The intervention group increased the accuracy of the measurements to 55% at 3 months and 70% at 6 months. At conclusion, the intervention group's mean difference in measurement from study staff decreased to 0.5 cm.

Lipman TH, Hench KD, Benyi T, et al. A multicentre randomised controlled trial of an intervention to improve the accuracy of linear growth measurement. *Arch Dis Child.* 2004; 89:342-346.

Editor's Comment: Growth is the single most important indication of a child's health.² Growth monitoring is an integral part of pediatric care. The American Academy of Pediatrics has recommended that height and weight be measured at least at birth; age 2-4 days; 1, 2, 4, 6, 9, 12, 15, 18 and 24 months; and yearly through age 21.³ It is disheartening that Lipman et al found high prevalence of incorrect techniques among pediatric and family practices. Even more disheartening is that 10% of pediatric practices and 40% of family practices did not measure children at every well-child visit.¹ This is a worldwide problem with a lack of equipment or trained personnel, inaccurate plotting

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