

with IGF-I, and then undergo granulocyte differentiation. 32D IGF-IR cells ectopically expressing IRS-1 grow indefinitely without differentiation. R<sup>-</sup> cells were also used to develop sister cells for comparison. R<sup>-</sup>/T cells express the SV40 large T antigen, while R<sup>+</sup> cells have the IGF-IR reintroduced. IRS-1 is mostly nuclear in IGF-I-stimulated R<sup>+</sup> cells and in R<sup>-</sup>/T cells, but cytoplasmic in the parental R<sup>-</sup> cells.

Using these 2 systems, the authors showed that IGF-I increased transcription from the rDNA promoter (ie, activated UBF1) in a time course compatible with nuclear translocation of IRS-1. Since UBF1 activation generally occurs via phosphorylation, additional experiments showed that UBF1 phosphorylation, mainly in the C terminus, was IGF-I stimulated and IRS-1 dependent. Beyond that, UBF1 regulation in the 2 cell models differed. In the myeloid cells deprived of IL-3, 32D IGF-IR/IRS-1 cells died without IGF-I, but maintained high levels of UBF1 protein when stimulated with IGF-I. The 32D IGF-IR cells (ie, without IRS-1) had high UBF1 protein levels, which dropped at 48 hours (ie, while the cells were still growing exponentially and not yet showing any morphologic signs of differentiation) and completely disappeared by the time the cells were differentiated into granulocytes. The drop in UBF1 protein was due to both decreased synthesis and increased degradation, though UBF1 mRNA levels remained unchanged. In the MEFs, cells that do not differentiate, UBF1 protein levels were stable after IGF-I treatment in both R<sup>+</sup> and R<sup>-</sup> cells. Thus, the authors concluded that IGF-IR/IRS-1 signaling regulates UBF1 activity, and hence the rDNA promoter, through phosphorylation and in some cells, through changes in protein level. UBF1 protein loss may

be related to the differentiation process, which tends to involve nucleolar dissolution.

Wu A, Tu X, Prisco M, Basergo R. Regulation of upstream binding factor I activity by IGF-I receptor signaling. *J Biol Chem* 2005; 280:2863-72.

**Editor's Comment:** *IGF signaling through the IGF-IR is understood to stimulate cellular survival and proliferation, and at the systemic level, growth. IGF-IR is a tyrosine kinase that is activated by ligand binding. Phosphorylation of tyrosine residues in IGF-IR recruits adaptor molecules like IRS-1 that then start kinase cascades, most notably the PI3 kinase/Akt pathways and the MAP kinase pathway (for reviews, see References 1-2). The paper by Wu et al adds another mechanism whereby IGF-IR signaling stimulates growth: activation of UBF1 through nuclear translocated IRS-1 and presumably PI3 kinase. UBF1 regulates RNA polymerase I activity at the rDNA promoter, thereby regulating the rate of ribosome biogenesis. Because ribosomes are required for protein synthesis, proliferating cells invest much energy in ribosome generation (reviewed in Reference 3). Without concomitant synthesis, proliferating cells would only become progressively smaller. Thus, growth involves increasing numbers of cells with maintenance of proper cell size, and IGF-IR is involved in regulating both these processes.*

Adda Grimberg, MD

## References

1. Vincent AM, Feldman EL. *Growth Horm Igf Res* 2002;12:193-7.
2. Dupont J, Pierre A, Froment P, Moreau C. *Horm Metab Res* 2003;35:740-50.
3. Moss T. *Curr Opin Genet Develop* 2004;14:210-7.

## Long-term Effects of Estrogen Treatment on Fertility in Tall Girls

Venn and colleagues identified from medical records 1248 Australian women who had been assessed and/or treated with estrogens (3mg DES or 150µg ethinyl estradiol daily) for tall stature during the years 1959 to 1993, to assess the effects of this treatment on long-term fertility. A group of 184 self-referrals (members of Tall Girls Inc an Australian advocacy group) were included in the study. To be included subjects had to have had a bone age determination at the time of assessment. Subjects were invited to complete a written questionnaire and computer-assisted telephone interview. The interview included questions regarding reproductive history including whether or not they had ever seen a doctor due to difficulty becoming pregnant, whether they had ever tried unsuccessfully for more than 12 months to become pregnant, and whether or not they had ever taken fertility drugs as treatment for infertility. The time to pregnancy was analyzed for each month of attempting pregnancy. Data from the medical records included age at menarche, treatment type, duration of treatment, and first and last assessment of estimated

mature height by Bailey and Pinneau method.

The final sample size included 618 women (75% of the treated and 95% of the untreated). The mean age of these women was 39.8 years (treated) and 37.7 years (untreated). Both groups were similar in terms of marital status and highest level of education. Self-reported current height was greater in the treated women (179.0cm vs 176.8cm). Both groups were similar in terms of history of smoking, oral contraceptive use, age of first sexual intercourse and lifetime number of male sexual partners. There were no differences between the women treated with DES or ethinyl estradiol on any parameter. Women who had been treated with estrogen were more likely to report problems with fertility. When the data were adjusted for age, the women who had been treated were less likely to have ever been pregnant and to have ever had a live birth. Treated women were more likely to have tried unsuccessfully for 12 months to become pregnant, to have seen a doctor because of difficulty becoming pregnant, and to have taken fertility drugs. Height was not related to fertility problems and the differences between

the 2 groups remained when the self-referred women were excluded from the analysis. A significant, but weak duration of treatment effect was observed.

The authors state that the data were not sufficient to establish a pathophysiological cause for the reduced fertility. They also state that the likelihood of ever becoming pregnant and having a live birth, although statistically reduced for women who had been treated for tall stature, was only slightly lower than that for untreated women and that newer treatments for infertility may reduce that difference.

Venn A, Bruinsma F, Werther G, et al. Oestrogen treatment to reduce the adult height of tall girls: long-term effects on fertility. *Lancet* 2004;364:1513-8.

**Editor's Comment:** Clearly there has been a significant drop in the number of girls seeking treatment to reduce

mature height potential over the past 20 years. However, the authors note that a recent survey of pediatric endocrinologists in the United States reveals that 23% have treated such girls over the past 5 years. Thus, although the absolute number of girls seeking treatment is low, such treatment is still being sought and is available. The current study, although not the first to show the possibility of adverse reproductive effects of estrogen treatment for tall stature, is perhaps the largest long-term follow-up to date. The information is interesting and important. Pediatric endocrinologists need to be able to discuss these facts with each family seeking to reduce their daughter's mature height potential. It is reassuring that no obvious safety concerns were identified through these interviews and chart data.

William L. Clarke, MD

## Micropenis: Long-term Follow-up

These authors report the long-term outcomes of 46,XY males with micropenis, but no other genital deformity, identified and treated intermittently with androgens or hCG during infancy, childhood and/or adolescence. Lee and Houk determined adult stretched penile length (SPL) and social adjustment in 20 patients with SPL  $<-2$  SD of normal at initial examination: 11 had hypogonadotropism and 3 primary testicular failure; in 6 patients no cause of the micropenis was identified. SPL increased in all subjects; adult SPL was  $>-2$  SD of the adult mean in 14 subjects and between  $-2.5$  and  $-2$  SD in 4; 2 patients had adult SPL  $<-2.5$  SD of the mean. Among these 20 patients and another 2 with micropenis first evaluated as adults, 21/22 were heterosexual; 8 were/had been involved in long-term heterosexual relationships. Relative to age-matched control subjects, those with micropenis (N=12 studied) had comparable findings in regard to heterosexual dating and sexual functioning, male friendships, education, employment, sports/leisure activities; none had a psychiatric illness. Despite normal adult SPL, 5 primarily obese patients stated that their penises were small. The investigators concluded that in adult men who had micropenis as children/adolescents: 1) 90% had adult SPL within the broad range of normal; 2) there was "reasonable social adjustment," no psychological pathology, and gender-appropriate sexual functioning.

Husmann evaluated adult SPL in 20 men with micropenis (here defined as SPL  $<-2.5$  SD of normal) diagnosed and treated during infancy in whom SPL did not increase appreciably despite multiple courses of testosterone. Five patients had a mutation in the androgen receptor, 6 had hypogonadotropism, and 9 had no known cause of the micropenis. Mean pretreatment SPL was  $-3$  SD (range  $-5.5$  to  $-2.6$ ) for age/race and mean adult SPL was  $-3.4$  SD (range  $-5.9$  to  $-2.2$ ).

All patients considered their penises to be small, and 5 had undergone (unsatisfactory) surgery to enlarge their penises; 19/20 were heterosexual; 12/20 men were sexually active, but 4 were incapable of vaginal penetration; 5 patients had mental illnesses requiring professional therapy. Despite these findings, Husmann concluded that these patients accept a male gender identity and many engage in a "satisfying heterosexual relationship."

Lee PA, Houk CP. Outcome studies among men with micropenis. *J Pediatr Endocrinol Metab* 2004. 17:1043-53.

Husmann DA. The androgen insensitive micropenis: Long-term follow-up into adulthood. *J Pediatr Endocrinol Metab* 2004.17:1037-41.

**Editor's Comment:** In the report of Lee and Houk, in 5/20 patients (1 hypogonadotropic subject, 1 with primary testicular failure, and 2 with "idiopathic" micropenis) SPL SD score did not appreciably increase between diagnosis and adulthood, but these subjects are not specifically discussed further, and their psychosocial status is unknown. It would have been of interest if Husmann had also reported his experience with the outcome of patients with micropenis responsive to testosterone. These data are reassuring in that they further demonstrate that there is no basis to consider sex reversal in the 46,XY male with micropenis as their gender identity is firmly masculine. Furthermore, with current surgical procedures for penile reconstruction, the opportunity for satisfactory penile enlargement has improved substantially.<sup>1</sup>

Allen W. Root, MD

## Reference

1. Jordan GH, Rosenstein DI, Gilbert D. *Growth Genet Horm* 2002;18:33-8.