

## Growth of Long-Term Survivors of Liver Transplantation

Viner et al performed a retrospective analysis of growth of 105 children who were long-term survivors of liver transplantation. During the 10-year period of the study, triple immunosuppression therapy using cyclosporine, azathioprine, and prednisolone was used. Height was recorded at all clinic visits using a Harpenden stadiometer. Following transplantation, height was recorded every 3 months for the first 18 months, twice a year for the next 3 years, and then yearly thereafter. Height is expressed as height Z scores (height SD scores) standardized against 1990 British growth references. Severe growth retardation was defined as a height below the 0.4 percentile. Continuous variables were analyzed by paired-tests and multiple regression analysis.

The height of patients at transplantation was significantly below that of the general population ( $P < 0.0001$ ), with the height Z score at -1.22. Following liver transplantation, height Z scores fell significantly in the first 6 months ( $P < 0.006$ ) but catch-up growth then occurred and was maximal from 6 months to 2 years. Height Z score at transplantation predicted 64% of the variance in height SDS at 2 years and 53% of the variance in height SDS at 5 years. Of 19 patients who were severely growth retarded, half remained so 4 years posttransplantation. Final height was recorded for only 14 patients, but their mean height SDS was -0.55. Diagnosis was not significantly associated with height Z scores at the time of liver transplantation ( $6.1 \pm 4.4$  years). Subjects undergoing transplantation who were less than 2 years old had significantly greater growth retardation at 6 months following transplantation ( $P < 0.05$ ) and a trend towards greater catch-up growth from 6 months to 2 years. Multiple regression analysis demonstrated that predictors for height Z scores at 6 months were initial Z scores and bilirubin at transplantation and prednisolone dose at 6 months. At 4 years, height Z scores were predicted by height Z scores at transplantation and the cumulative dose of prednisolone at transplantation. Age, sex, diagnosis, liver function at transplantation, cyclosporine dose, and the need for retransplantation were not predictive.

The authors state that this was the first report of long-term growth and final height after liver transplantation in children. They note

that their patients were a heterogeneous group and that transplantation in infancy was not associated with poor height outcome. The average final height after liver transplantation was on the 27th percentile. They suggest that further investigation of the use of corticosteroids prior to transplantation is needed, and that an attempt should be made to transplant children at earlier ages.

Viner RM, et al. *Arch Dis Child* 1999;80:235-240.

**Editor's comment:** This is an interesting and fairly complete retrospective analysis. A summation is in the box that follows. The authors point out 2 very important questions for further study. First, how can corticosteroid doses be minimized prior to the time of transplantation such that the cumulative dose would be less at that time? Second, what is the role of hepatic-derived growth factors in the findings? Whether exogenous growth hormone might have a role in preventing growth retardation prior to transplantation is an additional area for further study and speculation.

William L. Clarke, MD

### Key Findings of the Retrospective Analysis of 105 Long-Term Survivors of Pediatric Liver Transplants

- Average final height after liver transplantation was on the 27th percentile, although those undergoing transplantation as infants can achieve better final heights.
- Height at transplantation is the most important predictor of later height outcome, emphasizing the need for optimal transplant timing and preoperative nutritional management.
- High corticosteroid dose, poor liver function, and the need for a second transplant were associated with poor height outcome.
- Transplantation in infancy was not associated with poorer height outcomes.
- Normal pubertal progress was resumed 3 to 5 years after transplantation.

## Prolongation of Ovarian Lifespan Into Advanced Chronological Age By Bax-Deficiency

In both humans and mice, there is a marked excess of primordial ovarian follicles that degenerate early in life. The remaining oocytes appear to go through apoptosis over the lifetime of the individual female, leading usually during the fifth decade of life to menopause in women and to infertility 3 to 6 months before death in female mice. Bax-deficient female mice (ie, deficient in the normal Bax protein) have been found to have an increased number of primordial follicles in their ovaries compared with wild-type littermates. This excess of follicles is maintained into advanced age. In addition, the Bax-deficient mice possess hundreds of ovarian follicles that are in different stages of development. The aged Bax-deficient females fail to become pregnant. However, it appears that this is due to failure of the pituitary axis rather than nonfunctional oocytes because these mice can be superovulated and oocytes remain that are competent for in vitro fertilization. This suggests that the increased number of oocytes are competent for producing embryos even though assisted reproductive technology may be needed in old age. Careful morphometric analysis

shortly after puberty of the numbers and structure of nonatretic follicles in wild-type and in Bax-deficient mice revealed approximately 3 times the number of nonatretic primordial follicles in the latter, suggesting that Bax-deficient mice do not go through the normal apoptotic process seen in normal mice and normal human females.

Perez GI, et al. *Nature Genet* 1999;21:200-203.

**Editor's comment:** This observation in Bax-deficient mice has enormous ramifications for infertile women and suggests that there may be a mechanism to maintain oocytes in Turner syndrome and some familial types of ovarian degeneration. Perhaps developing a block to the normal Bax protein could maintain normal viable oocytes. Fortunately, this manipulation should be possible in mice and yet have great application in humans.

Judith G. Hall, MD