

active beta cells, and active beta cells have been shown to be more susceptible to cytokine-induced damage than resting cells in vitro.

Hyponen E, et al. *Diabetes Care* 2000;23:1755-1760.

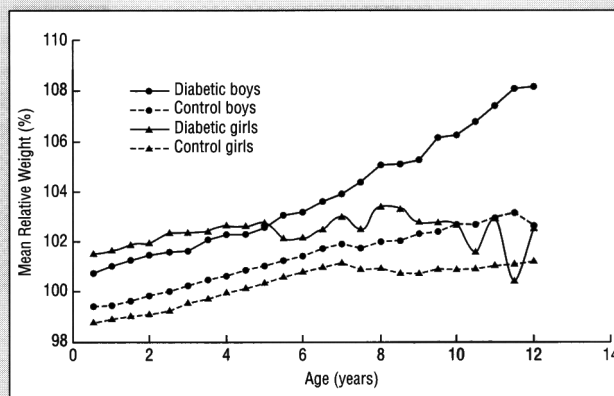
Editor's comment: This is a very interesting and important article. The incidence of type 1 diabetes in Finland is exceedingly high, much higher than that in the United States. The association of early childhood obesity and increases in relative height with an increased incidence of type 1 diabetes is significant information and a warning to the pediatric community. Recent reports have documented a significant increase in the incidence of type 2 diabetes among children and adolescents, paralleling the increase in obesity in this group. Hyponen et al's paper is the first to show that an increase in weight also is associated with an increase in type 1 diabetes. The information regarding tall stature is not new, but is consistent with other reports from Europe and the United States.

The Childhood Diabetes Study Group in Finland has presented information that needs to be transmitted to all physicians caring for children. The prevention of childhood obesity may be one of the most important therapeutic activities of pediatricians.

William L. Clarke, MD

Figure

Cross-Sectioned Mean Relative Weights for Diabetic and Control Groups, Calculated from the Interpolated Values



Reprinted with permission from Hyponen E, et al. *Diabetes Care* 2000; 23:1755-1760.

Neonatal Outcome After Preimplantation Genetic Diagnosis by Analysis of the Polar Bodies

New reproductive technologies have increased the options available to couples. Preimplantation genetic diagnosis (PGD) was developed for couples at high genetic risk to avoid establishing pregnancies with genetic diseases. PGD is performed by blastomere biopsy or polar body removal (PBR) for mendelian or chromosomal disorders. Mothers who are heterozygotes for a mutation are good candidates for this procedure. Primordial germ cells will contain 1 chromosome carrying the affected allele and another carrying a normal allele. During meiosis, the oocyte will double its genetic material, yielding 2 chromosomes with normal alleles and 2 that contain the mutant allele. At the conclusion of meiosis I, the oocyte extrudes half of its chromosomes in the form of the first polar body. When the first polar body is removed before fertilization, it can be analyzed for the presence of the normal or mutant allele. Subsequently, fertilization occurs, the oocyte completes a second meiotic division, and then the second polar body is extruded containing 1 set of chromosomes. The second polar body also can be analyzed, and it will usually be identical to the 1 that remains in the egg. If a crossover occurs during meiosis, the first polar body may contain both mutated and normal alleles, in which case it will be necessary to analyze the second polar body to see which allele will be left in the fertilized egg. It is therefore possible to identify embryos developing from oocytes that contain a normal allele and then to transfer the fertilized oocyte back to the mother and establish a pregnancy.

The present study is the follow-up of the first 97 pregnancies that yielded 109 live-births after PGD by PBR and assessment. Ninety-one infants were born where analysis had been done for chromo-

somal disorders, and 18 infants were born where analysis had been done for mendelian disorders (including cystic fibrosis, sickle cell disease, long-chain acyl-CoA dehydrogenase deficiency, and thalassemia). All case analyses also were done postnatally to confirm the prenatal diagnosis. Birth data are available for 98% of the cohort, and developmental assessments are available for 44 children older than 6 months of age (see Table, page 31).

There were 80 singleton pregnancies, 9 twins, and 7 triplets, of which 3 were reduced to twins. One gestation with 5 fetuses

GROWTH, Genetics, & Hormones is published under an educational grant from Genentech, Inc. The information reflects the views of the editors and/or contributors and not necessarily those of the sponsor, grantor, or the publisher.

Published by:

SynerMed
Communications

405 Trimmer Road
PO Box 458
Califon, NJ 07830

Editorial Board

Chairman

Robert M. Blizzard, MD
Charlottesville, Virginia

Associate Editors

William L. Clarke, MD
Charlottesville, Virginia

Judith G. Hall, OC, MD
Vancouver, BC, Canada

William A. Horton, MD
Portland, Oregon

Fima Lifshitz, MD
Miami, Florida

Allen W. Root, MD
St. Petersburg, Florida

© 2001 SynerMed Communications (01GN200D). All rights reserved.

miscarried in the first trimester. There was an increased occurrence of prematurity, and 1 neonate died as a result of placental abruption. The mean singleton birth weight was at the 47th percentile, and the mean singleton birth length was at the 57th percentile. Forty percent of births were by cesarean section, which is comparable to other in vitro fertilization (IVF) studies. There were 6 infants with birth defects: 1 with a unilateral transverse limb reduction (amniotic band syndrome); 1 with neonatal seizures who had 3 cerebral infarcts on imaging; 1 with a minor hemangioma; 1 with minor strawberry hemangiomas on both arms; 1 with thickening of the tricuspid valve that did not require surgery; and 1 with bilateral webbed toes. Only 1 child of the 44 who had been followed up to 6 months of age was reported to have developmental delay. This was 1 of twins who had had no perinatal complications. This child had speech delay and was receiving speech therapy. This frequency of birth defects is certainly not out of line of what would be expected.

The financial cost of PGD by PBR is reported to be \$8500 for 1 typical cycle. Diagnostic testing for mendelian traits may involve as much as another \$1000 in laboratory costs.

The authors point out that in addition to the financial costs, there are some intrinsic risks of multiple gestations and the complications associated with them. Nevertheless, polar body prenatal diagnosis does provide families with another option in terms of prenatal diagnosis.

Strom CM, et al. *Pediatrics* 2000;106:650-653.

Table
Summary of Preimplantation Genetics
Pregnancies

Number of Fetuses	Number of Pregnancies	Number of Spontaneous Abortions	Number of Live Births
1	80	5	75
2	9	1	16
3	7	0	18*
5	1	1	0
Total	97	7	109

*Three couples had reduction to twins; 4 couples delivered triplets.

Reprinted with permission from Strom CM, et al. *Pediatrics* 2000;106:650-653

Editor's comment: The data from this large center are reassuring. The reliability of testing for mendelian disorders needs further study since there are really only 18 cases. The procedure certainly allows individuals to obtain a diagnosis before implantation, if that fits with their particular ethical stance. Clearly, the cost is much higher than that associated for prenatal diagnosis which is performed later in pregnancy. However, it does not involve termination of pregnancy, and only those embryos which do not have a detectable abnormal test would be used for implantation. The reader may wish to extend his/her knowledge of this alternative diagnostic technique as it undoubtedly will become a common tool of IVF.

Judith G. Hall, OC, MD

Spectrum of the Tricho-Rhino-Phalangeal Syndromes

Three types of tricho-rhino-phalangeal syndrome (TRPS) have been clinically defined. The features characterizing these syndromes, but described initially in TRPS I, include sparse, slowly growing scalp hair; sparse eyebrows laterally; bulbous tip of the nose; protruding ears; brachydactyly and mild to moderate short stature; and the presence of cone-shaped epiphyses of the middle phalanges on X-ray films. TRPS II is distinguished from TRPS I by the occurrence of exostoses; mental retardation often is present. TRPS III is distinguished by the greater severity of the characteristics of TRPS I.

Mutations of a gene designated *TRPS1*, which encodes a zinc finger transcription factor, were recently identified in patients with TRPS I. Microdeletions of chromosome 8q24.1 that include both *TRPS1* and *EXT1*, the gene mutated in hereditary multiple exostoses type I, are responsible for TRPS II. The current study by Lüdecke et al was done to determine if TRPS III is due to *TRPS1* mutations, representing the severe end of a clinical spectrum of TRPS I, or, alternatively, results from mutations of another gene. The results confirmed the former possibility and demonstrated a correlation between the type of mutation and the severity of clinical phenotype.

TRPS1 was screened by direct sequencing of the coding and flanking intron sequences for mutations in 79 patients with TRPS, including 57 unrelated individuals with either TRPS I or

TRPS III. Thirty-five different mutations were found in 44 of 51 unrelated patients. The majority were deletions or disruptions, nonsense and splicing mutations. These would be expected to truncate the transcription factor protein, leading to loss of function, since the resulting proteins would lack a nuclear localization signal needed for nuclear entry and the C-terminal zinc finger domain required for dimerization. These mutations would, therefore, act through haploinsufficiency. Missense mutations were identified in 8 cases. They all mapped to exon 6, which encodes the GATA zinc finger domain necessary for DNA binding. The resulting proteins would be expected to enter the nucleus and form complexes with other transcription factors that would function poorly because of defective DNA binding. They are predicted to exert a dominant negative effect, which as a disease-causing mechanism generally has a greater impact than haploinsufficiency.

The patients also were evaluated clinically, mainly in terms of height and severity of brachydactyly as judged from hand X-rays films. The results showed a continuous spectrum of severity. They further revealed that nonsense and disruption mutations, which would be predicted to cause haploinsufficiency of *TRPS1*, were associated with the range of severity typical of TRPS I. In contrast, the missense mutations predicted to act in a dominant negative fashion correlated with the severe end of the spectrum characteristic of TRPS III.