

The authors conclude that their data suggest that the sexual dimorphism in the regulation of leptin and IGF concentrations, which previously was demonstrated in later childhood, may already be established at birth. They also suggest a possible role for leptin and/or the IGF-I system in relation to birth size and to the risk of diseases such as non-insulin dependent diabetes and cardiovascular disease which have been shown to be frequent in low birth weight infants.

Vatten LJ, et al. *Pediatrics* 109:1131-1135.

Editor's Comment: *These findings have important implications for understanding the relationship between low birth weight and adult morbidity - especially*

cardiovascular disease, hypertension, and type 2 diabetes. It would appear that leptin, IGF-I, and IGFBP-1, which have been shown to be important factors in growth in utero, may be important in understanding the risk of developing these adult diseases. It would be very important to follow a cohort of children from birth through adulthood with serial measurements of IGF-I, IGFBP-3, and leptin in order to better understand how these factors change over time and how they might contribute to the development of serious adult disorders. Studies such as those by Vatten et al in Norway support the importance of conducting such difficult epidemiological studies.

William L. Clarke, MD

A Longitudinal Study of the Effects of a Gluten-Free Diet on Glycemic Control and Weight Gain in Subjects With Type 1 Diabetes and Celiac Disease

Amin et al from Oxford reported their findings of longitudinal growth characteristics and glycemic control in children with type 1 diabetes along with celiac disease (CD). Annually, from 1994 and 1998, 230 children with type 1 diabetes were screened starting in the first year after the onset for the presence of IgA and anti-endomysial antibodies (EMA). A total of 10 children were EMA positive and another one was AGA positive, which was 4.8% of the clinic population. Only one patient demonstrated symptoms typical of CD, including failure to thrive and steatorrhea; four complained of some mild abdominal discomfort. Jejunal biopsy showed classical histopathology of CD in all eleven patients. These subjects were matched for age, sex, and diabetes duration with two control diabetic children who were negative for EMA. Height, weight, and HbA_{1c} were measured at the time of diagnosis of CD and every 3 months. Antibody levels were tested every 3 months until negative, and then yearly. The ANOVA model was used to determine the influence of CD on both HbA_{1c} and BMI SDS. The data are presented as mean \pm SEM.

Mean BMI SDS in the CD group was significantly lower (-1.2 ± 0.1 vs. -0.1 ± 0.1 , $P=0.005$), as was mean weight SDS (-0.7 ± 0.3 vs. 0.5 ± 0.3 , $P=0.002$) than in those without CD. However, there was no difference between the two groups mean height or C-peptide level. Mean age of diagnosis of CD was 11.2 years (2.2-17.3). The mean duration of diabetes at diagnosis was 3.8 years (0.9-7.2). Mean HbA_{1c} was significantly lower at diagnosis in the children with CD ($8.9\% \pm 0.3\%$ vs. $9.8\% \pm 0.3\%$, $P=0.002$), but there was no difference in the mean daily insulin dose in the two groups. The difference in mean BMI SDS between the subjects and the controls was eliminated by 12 months of gluten-free diet (1.1 ± 0.13 vs. 1.0 ± 0.1 , $P=0.11$). HbA_{1c} levels were lower

than in the controls during the period of gluten-free diet (8.3 ± 0.2 vs. 10.0 ± 0.2 , $P=0.002$). Insulin requirements increased in both groups, but no difference in those requirements developed between the two groups. Using a general factorial linear model, CD was associated with lower BMI SDS and lower HbA_{1c} across time, independent of other factors such as insulin dose and regime. Also, while on a gluten-free diet, the children with CD had lower HbA_{1c} which was independent of BMI SDS or the insulin dose or regimen. The EMA antibodies tended to disappear while the patients were on the gluten-free diets.

The authors reviewed recent reports regarding the association in children between type 1 diabetes and CD. Prevalence rates range between 1.7 to 10%. However the data on whether intervention with gluten-free diet would be of benefit remain controversial. This is, in part, because there are few longitudinal follow-up data and few age and sex matched controlled studies. The authors note that their findings could have been influenced by the small sample size or the increased input by dieticians which was received by case subjects. They stress, that because the long-term complications of CD include gastrointestinal malignancy, lymphoma, infertility, and osteoporosis, the screening of children with type 1 diabetes at a young age may be cost effective and warranted.

Amin R, et al. *Diabetes Care* 25:1117-1122.

Editor's Comment: *These findings are very intriguing. Many pediatric endocrine clinics are now screening children with type 1 diabetes for EMA or tissue transglutaminase IGA to identify CD. There is controversy as to whether or not children who are*

asymptomatic with their CD will benefit from a gluten-free diet, and whether or not there is any effect of a gluten-free diet on the management of their diabetes. Amin and co-workers have demonstrated that indeed children with CD and type 1 diabetes are anthropometrically different from those children without CD, and that treatment reverses this finding. In addition, there appears to be a treatment benefit on overall glucose control. The authors noted that their data could

have been influenced by the frequent visits to the dietician by case subjects. It will be important to determine whether gluten-free diet is of benefit in all children with diabetes, and or whether similar nutritional input to all type 1 diabetic children could improve HbA_{1c} to the extent observed in this study.

William L. Clarke, MD

Risk for Abnormal Outcomes is Increased with Assisted Reproductive Technology

The advent of assisted reproductive technologies (ART) has increased the complexity of care in newborn nurseries. An increased number of premature infants and multiple births are among a variety of risks that occur with the increased frequency of ART. These risks should be shared with all perspective parents (patients).

An article by Schieve et al studied 42,463 infants who were born between 1996 and 1997, and who had been conceived utilizing ART. These infants were compared to the three million plus infants born in the United States during that period. Among singleton births conceived by ART, and born at 37 weeks or after, the risk for low birth weight was 2.6 times that in the general population. The use of ART was also associated with an increased rate of multiple births which also increases the rate of IUGR births and many other complications.

Hansen et al reported on 301 infants conceived by intracytoplasmic sperm injection and 837 infants conceived with in vitro fertilization (IVF). These were compared to naturally conceived infants from the same region. The infants conceived with ART had an increase of birth defects which was greater than double the occurrence among the naturally conceived. The abnormalities involved a broad spectrum of congenital anomalies. The etiology for the increased risk was unclear. However, advanced maternal age, the usual underlying causes of infertility, medications used to induce ovulation and maintain pregnancy, factors associated with procedures such as freezing and thawing of embryos, and delayed fertilization of the oocyte individually or collectively, contributed to this increased risk.

Strömberg et al studied the neurologic sequelae of children born after IVF. Through a population based retrospective cohort assessment, they compared the neurologic outcome of 5,680 children born after IVF against the neurological outcome of 11,360 matched controls. For each of the 2,060 twins born after IVF, a second set of twin controls was used. Children born after IVF demonstrated an odds ratio of 1.7 of needing habilitation services. Among singletons born after IVF,

the risk was 1.4. The most common neurologic disorder was cerebral palsy, with a relative risk of 3.7 for all children born after IVF and 2.8 for singletons. Data concerning twins born after IVF was essentially the same as control twins in respect to neurologic sequelae. Twins with low birth rate and prematurity were more likely to require habilitation services. Maternal age did not seem to be a factor in this study.

Multiple births have an increased risk factor for neurologic sequelae and, consequently, Ozturk et al. strongly recommend that no more than two embryos be placed in the uterus while performing IVF.

Hansen, et al. *N Engl J Med* 2002;346:725-730.

Ozturk, et al. *Lancet* 2002;359:232.

Schieve, et al. *N Engl J Med* 2002;346:731-737.

Strömberg, et al. *Lancet* 2002;359:461-465.

First Editor's Comment: Information regarding the increased risk of problems associated with ART must be shared with the families who are considering using them. Healthcare providers must also be aware of these risks. The increased expenditures associated with ART are not just the cost of the procedure, but also involve the long-term health care costs. Healthcare costs have become more expensive because of these complications, and these are not usually considered when assessing the expenditures of ART.

Judith G. Hall, OC, MD

Second Editor's Comment: A dictum of physics is only rarely violated. Specifically every positive force has a negative force and vice versa. Chances are what we take daily. There are no positive assurances about anything except death. Therefore, we should expect that every technology will not be perfect – either in construction of the technology itself, or carrying out of a procedure with the technology and in the results thereof. Thus, we should not be disturbed by some imperfections of the system, although we should continue to try to make it perfect.