

The authors concluded that interventions to improve the zinc nutriture of children should be considered in populations at risk of zinc deficiency, especially and particularly in those where there are elevated rates of children who are underweight or experience stunting.

Brown KH, et al. *Am J Clin Nutr* 75:1062-1071.

Editor's Comments: *The benefits of zinc supplementation for children's growth have been debated for many years. This meta-analysis conducted by Brown et al showed that zinc supplements probably are of benefit for children in developing countries. It is not surprising that in such populations there are nutrient deficits which can be corrected by specific nutrient supplementation. Underlining the potential nutritional deficiency status of the population studied and reported, there was a higher significant aggregate zinc effect on children's growth in those who exhibited deficits of body weight for height. It might also be inferred that children who do not exhibit growth retardation or body weight-for-height deficits might not be nutrient-deficient, and may, therefore, not benefit from zinc supplementation. It should also be kept in mind that zinc deficiency is difficult to document, and that zinc supplementation, either alone or in combination with other nutrients, is*

not easily accomplished nor tolerated by children. Zinc supplements are also expensive where they might be needed the most, namely in developing countries. The foods richest in zinc are from animal sources which are also often not accessible in these countries. Children in the United States and other developed countries who ingest a wide variety of meat products are highly unlikely to be zinc deficient.

I agree with the authors who state in the last paragraph of this article "Because of the important functional consequences of zinc deficiency for children's growth and other health outcomes, interventions to improve zinc nutriture should be considered in those populations at particularly high risk of zinc deficiency. Additional research will be needed to determine whether the mean serum zinc concentration of a population is a useful predictor of response to zinc supplementation. On the other hand, the population mean serum zinc concentration does increase after supplementation, so this measure can be used to indicate whether public health interventions to promote increased zinc intakes are successful." For those interested in this topic, reviewing the original manuscript and its excellent and extensive graphic expression of data will be appreciated.

Fima Lifshitz, MD

Placental-Specific IGF-II is a Major Modulator of Placental and Fetal Growth

A substantial proportion of imprinted genes, i.e., genes expressed from only one parental chromosome, are involved in placental development and fetal growth in mammals. In the mouse for example, *Igf2* is expressed paternally in the placenta and fetus, while its receptor is expressed maternally. Imprinted genes can act directly on the fetus by influencing cellular proliferation and apoptosis; they can also affect fetal growth by influencing placental structure and physiology and the supply of maternal nutrients. Debate over the evolutionary significance of imprinting in mammals has led to the so-called genetic conflict hypothesis or theory of imprinting. It predicts that paternally expressed genes act on the placenta to promote extraction of resources from the mother to enhance fetal growth while maternally expressed genes act to restrain fetal growth to conserve maternal resources for long-term reproductive fitness of the mother. Testing this hypothesis has been difficult because the relevant genes are expressed in both placenta and fetus and their tissue-specific inactivation has not been achieved.

Recently, it has been shown that the mouse *Igf2* has four promoters, one of which, designated P0, directs paternal expression of *Igf2* in the labyrinthine trophoblasts of the placenta. Deleting this promoter

through gene targeting enabled Constância and colleagues to study the impact of paternally-directed placental IGF-II on fetal growth. The P0 knockout for *Igf2* was confirmed by in situ hybridization that revealed a marked reduction of *Igf2* expression specifically in the labyrinthine trophoblasts. Expression of *Igf2* from its other promoters was normal in mutant placentas and fetal tissues as were levels of IGF-II in the fetal circulation.

Lack of the P0 *Igf2* transcripts with paternal transmission primarily resulted in placental growth restriction, which was detected early in gestation at embryonic day 12 (E12) of the 19-day mouse gestation. The impaired growth of the mutant placentas remained relatively constant throughout the remainder of the pregnancy (weight of mutant placentas 76%, 82%, 68%, 68% of normal at E12, E14, E16, E18, respectively) suggesting that the paternally-directed, labyrinthine trophoblast-specific *Igf2* transcripts are required to sustain normal growth of the placenta.

In contrast to the early decrease in placenta size, the indirectly affected fetuses became growth restricted only toward the end of gestation. Their weight was 96% of normal at E16, but dropped to about 70% at birth. The ratio of fetal to placental weight increased as

gestation proceeded and was significantly higher for mutant compared to normal pregnancies reflecting the small placenta size.

To address the discrepancy between placental and fetal growth, the authors compared normal and mutant placentas structurally and functionally. Other than size, no obvious differences in tissue organization or cell morphology were detected. They next compared maternal-fetal transport of different radiolabelled compounds, one transferred by passive diffusion and the other by active transport. Their results showed that passive diffusion declines proportionate to the relative reduction in placental size. Active or system A transport, however, increases during mid gestation, apparently compensating for the loss of passive transfer until near the end of gestation when this compensation is insufficient to meet the needs of the fetus and fetal growth drops off. Importantly, the system A transporter has been shown to be a determinant of fetal growth.

In summary, deletion of a placental-specific imprinted transcript results in fetal growth restriction, primarily through a decrease in total nutrient transfer across the placenta. This example of a morphologically normal but small placenta affecting fetal growth supports the genetic conflict theory of imprinting, in which a placental-specific gene expressed from the paternal allele regulates the supply of nutritional resources to the fetus. On the other hand, fetal demand for nutrients is genetically regulated by the level of growth factors such as IGF-I and IGF-II. Increasing fetal size therefore requires a higher level of demand (for example, higher fetal IGF-II) as well as a higher level of supply (by increasing, for example, placental surface area). Reduced fetal size can be the outcome of reduced supply (as in the P0 mutant described here) or of reduced demand (for example *Igf1* knockout, which reduces fetal but not placental size). The mouse *Igf2* gene is remarkable in combining the

control of both the supply and the genetic demand for maternal nutrients in a single gene.

Constância M, et al. *Nature* 2002;417:945-948.

First Editor's Comment: *This work supports the genetic conflict theory of imprinting showing that placental-specific genes expressed from the paternal allele contribute substantially to the supply of nutrients a fetus receives from its mother. It also shows that the placenta can partially compensate at least for the loss of this paternal effect. It will be interesting to learn more about the nature of the compensation, which represents a potential mechanism to exploit in treating intrauterine growth retardation. It is important to acknowledge, that the relationship between mother and fetus differs substantially between mice and humans, especially with regard to size and duration.*

William A. Horton, MD

Second Editor's Comment: *As a pediatric endocrinologist who has had a special interest in IUGR for many years, I found the reading of the original article most informative. Not mentioned in the abstract or First Editorial comment was the following brief statement, "At birth, P0 mutant pups were 69% of normal birth weight. This was followed by postnatal catch-up growth which was complete by three months of age." While, as Dr. Horton stated above that mice and humans (may) differ substantially, there is a corollary between the catch up growth in these IUGR mice and the catch up growth that is seen in most IUGR human neonates (primarily those without associated dysmorphology) in the first two years of life. Subsequent studies dealing with the genetic conflict theory in humans should be very informative and intriguing.*

Robert M. Blizzard, MD

Insulin-like Growth Factor I and Leptin in Umbilical Cord Plasma and Infant Birth Size at Term

Umbilical cord blood samples were collected from 12,804 consecutive deliveries, and cord plasma samples were collected from 585 singleton infants born in Norway at term after uncomplicated pregnancies. These were analyzed for plasma leptin, IGF-I, IGFBP-1 and IGFBP-3. Data were analyzed following log transformation of IGFBP-1 and leptin values. Linear regression analysis was used to determine the contribution of maternal and infant factors to umbilical levels of these hormones. The mean age of the mothers of these infants was 28 years. Seven percent had smoked at the beginning of the pregnancy, and 36 percent were primiparous. Male

infants had a higher birth weight and length than girls, but girls had a higher ponderal index. Leptin and IGF-I levels were higher in the cord blood of female infants than in males. None of the maternal factors which were analyzed, including pre-pregnancy weights, smoking, or number of previous pregnancies were significantly associated with levels of cord leptin. IGF-I, IGFBP-3, and leptin increased proportionately with increasing birth weight. Levels of IGF-I and leptin were the strongest predictors of both birth weight and birth length, and were independent of length of gestation, maternal age, parity, pre-pregnancy weight, smoking and offspring sex.