Intrauterine nutrition and adult disease

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Professor Barker and colleagues have published a large series of epidemiological studies showing that body size and shape at birth are strong predictors of the subsequent risk of developing several adult diseases including coronary artery disease, hypertension, chronic lung disease and non-insulin dependent diabetes. These effects of birth phenotype are independent of other known risk factors, and grow stronger with increasing age. We have put forward the hypothesis that intrauterine nutrition determines birth phenotype, and it also determines the programming of a number of key homeostatic systems in a way which predisposes to adult disease. Thus the association between birth phenotype and adult disease is determined by nutrition of the fetus before birth. Although the mechanisms are not yet known, animal studies are beginning to demonstrate that intrauterine nutrition does affect fetal growth, cardiovascular and metabolic status. Intrauterine nutrition also may have effects that last over more than one generation.

There is extensive evidence from animal studies that intrauterine nutrition affects birth phenotype. In sheep, severe maternal undernutrition for just 10 days in late gestation (term = 145 days), results in fetuses with greatly enlarged hearts and kidneys, but small lungs. Maternal undernutrition around the time of conception results in a fetus that grows relatively slowly in late gestation and is partially protected from these effects. Development of coronary artery walls may also be altered by the same maternal nutritional insult.

We also have evidence in fetal sheep studies that intrauterine nutrition affects fetal metabolism and cardiovascular status. Slowly growing fetal sheep are relatively insulin resistant *in utero*. Fetuses undernourished for 10 days in late gestation develop hypertension during the 10 days of refeeding. Preliminary results also suggest that the relationship between birth size and blood pressure persists in lambs for at least the first few months after birth.

The effects of intrauterine nutrition are not just confined to later life of the affected fetus. Rats marginally undernourished for seven generations take three generations of nutritional rehabilitation to reach the size of control animals. Those re-fed at weaning in the first generation may become obese. Similarly, in human studies severe maternal undernutrition in early pregnancy has been associated with an increased rate of obesity in the offspring. Reports from the Dutch famine suggest that baby girls exposed to undernutrition *in utero* in early gestation themselves give birth to small babies. Thus the effect of intrauterine undernutrition may extend over at least two generations, making interpretation of some genetic studies very difficult.

Intrauterine nutrition clearly affects fetal growth, metabolic and cardiovascular status before birth. These effects may persist after birth and even over subsequent generations. The mechanisms by which intrauterine nutrition predisposes to adult disease remain to be explored.

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