Small-Baby Biology

Mechanisms of fetal growth retardation are being explored in animal as well as human studies

By JULIE ANN MILLER

Second of two articles

The normal course of fetal development can be thwarted by a multitude of factors — originating in the mother or the fetus itself. When these adverse conditions result in retarded fetal growth, the infant is often at higher than normal risk for problems at birth and later in life. While medical researchers are eager to develop methods to detect intrauterine growth retardation and to treat the fetuses, therapeutic measures will be difficult to develop and evaluate until the investigators better understand the various factors involved in producing small-for-gestational-age babies and the reasons behind their developmental difficulties.

Maternal factors appear to be most often responsible for the depressed rate of fetal growth, David R. Cox of tte University of California at San Francisco told a recent meeting at the National Institute for Child Health and Human Development in Bethesda, Md. He speculates, "While maternally controlled restraint of fetal growth could be due to either limitation of space, limitation of essential nutrients, or restricted transfer of nutrients from the mother to the fetus, restriction of nutrient transfer is probably the most important factor in humans."

The cellular mechanisms by which maternal genetic factors limit transfer of nutrients from the mother to the fetus are essentially unknown. Cox suggests maternal genes may control the development of the blood supply to the placenta and the fetus's supply of hormones and growth factors.

Small fetuses tend to have small placentas, so blame for growth retardation is often fixed on the placenta. But it is not certain what is cause and what is effect. "I am not impressed with the prognostication from the size of the placenta to the size of the fetus ... nor do I believe that 'placental insufficiency,' as it is used in common parlance, exists at all," says Kurt Benirschke of the University of California School of Medicine at San Diego.

Some placental characteristics that have been associated with intrauterine growth retardation, according to Benirschke, are absence of one umbilical artery, disease-related changes in the placental vascular bed in hypertensive toxemia, some inflammatory conditions, and a condition in which the placenta is small, thick and its characteristics suggest abnormal implantation. In addition, Benirschke has detected proteins characteristic of herpes viruses in the placenta of newborns with a variety of problems, including intrauterine growth retardation.

One possible cause of intrauterine growth retardation is that during pregnancy a woman's blood vessels are only incompletely transformed into arteries capable of supplying blood to the uterus and placenta, according to F. Van Der Veen and H. Fox of the University of Manchester in England. Their microscopic studies suggest that placentas of small-for-gestational age infants may receive insufficient oxygen. They therefore suspect that the primary cause of fetal growth retardation is generally not placental damage but rather restricted blood flow from the mother.

Another likely candidate as a cause of intrauterine growth retardation is maternal nutrition. Historical data support a direct relationship between diet and fetal growth. During the Dutch famine of 1944-1945, the overall drop in birthweight in the previously well-nourished Dutch population was about 200 grams. Infants born during the siege of Leningrad, 1941-1944, showed an even greater reduction in birthweight, about 400 grams.

Yet, in the United States today most mothers of small-for-gestational-age babies do not appear to be grossly malnourished, says Jack Metcoff of the University of Oklahoma in Norman. If fetal growth is modulated by maternal nutrition, then some sort of subtle malnourishment, for example a nutrient imbalance, must be present, Metcoff says.

To find the underlying causes of fetal growth retardation, and to develop treatments for it, many researchers have turned to animal experiments. There, scientists can apply treatments that may improve the outcome of a pregnancy and indicate promising approaches for human obstetrics.

In pigs there is a natural model for intrauterine growth retardation — the fetuses at the far end of the uterus appear to receive less nourishment and are born the runts, substantially smaller than their littermates, although brain development lags less than does body size.

Nathanielsz

These lambs were born on the same day of different ewes. Although the lambs were the same gestational age at birth, one is small due to experimentally caused intrauterine growth retardation. It was induced by removing from the ewe's uterine lining before the pregnancy most of the sites at which placenta forms.

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Fetal growth retardation may occur among animals, as in the case of the 27-gram collared lemur, called Chiclette, born in April at Duke University (SN: 5/28/83, p. 350). Normal lemur birth weight is 70 to 80 grams. Like many small human infants at birth, Chiclette's head (inset) appeared disproportionately large and she had little fat. The growth retardation may have been due in part to the mother's advanced age. In addition, some of the mother's uterus may have been removed years ago in Madagascar. Now six months old (immediate right), Chiclette weighs more than 500 grams and is within the normal weight range, although she still is "on the small end for a kid her age," says Andrea Katz of the Duke Primate Center.

Rats, sheep and monkeys have been most extensively used in animal experimentation. Because it would be impractical for scientists to wait for these laboratory animals to have natural growth-retarded fetuses, they induce intrauterine growth retardation in several ways. These include restricting the diet of the pregnant animal, constricting blood vessels going to the placenta and fetus and decreasing the size of the placenta.

Researchers may need to study several animal systems to answer questions about intrauterine growth retardation, suggests Peter Nathanielsz of Cornell University in Ithaca, N.Y. Different methods of induction may mimic different causes of intrauterine growth retardation; for example blocking arteries may more closely resemble insufficient blood supply to the human placenta, while nutritional deficiencies may mimic human malnutrition. In addition, he says, "From a detailed appreciation and knowledge of species differences we can gain insights into underlying basic physiological and biochemical principles."

Sheep are commonly used because dramatic changes in the maternal circulatory system during pregnancy are similar to those of humans. The heart's output approximately doubles and the blood flow is redistributed. The share going to the uterus, normally 0.5 percent of the heart's output, is increased to 16 percent by the end of the pregnancy. Experiments on sheep have demonstrated that different natural compounds, such as the hormone angiotensin II, can alter uterine and placental blood flow.

The metabolism of the fetal lamb has been widely studied using a "balance-sheet approach," says John Sparks of Colorado Health Sciences Center in Denver. During maternal starvation, for example, influx of sugars to the fetus decreases and fetal breakdown of amino acids increases. Scientists are now looking at the metabolic response of individual fetal organs — brain, heart, gut, liver and hindlimb. Fetal liver, for example, can respond to maternal starvation by producing and releasing glucose.

Often ignored in metabolic studies, the placental metabolism is crucial in supporting a pregnancy. Sparks says the placenta consumes a major portion of the nutrient supply provided by the mother. In fetal lambs, approximately 50 percent of the oxygen and 75 percent of the glucose put into uterine circulation by the mother is consumed by the uterus and placenta; the metabolic rate of the placenta is approximately as high as that of the brain.

Rhesus monkey experiments indicate that deficiency of oxygen is not the primary factor in at least one model of intrauterine growth retardation. While decreasing uterine blood flow does result in intrauterine growth retardation, it does not decrease the fetus's uptake of oxygen until the uterine flow falls extremely low. Charles Rosenfeld of the University of Texas in Dallas says, "Uterine oxygen delivery far exceeds fetal needs. There is an enormous margin of safety."

An exciting possibility for therapy in pregnancies with intrauterine growth retardation was described at the NICHD meeting by Valery Charlton of UC San Francisco. If the retardation is caused by an inadequate flow of nutrients from the mother to the fetus, it should be possible to give the fetus supplements. Charlton reports that she has prevented intrauterine growth retardation in sheep by supplying glucose and nitrogen to the fetus by continuous infusion through a tube into the fetal gastric system.

Early in the third trimester, Charlton restricted the diet of pregnant sheep to the amount of alfalfa that would maintain their weight but prevent further weight gain. At birth the animals that had received the supplementary glucose and nitrogen as fetuses were nearer to normal weight and brain/body proportion than were those that had not had the supplement. "Fetal supplementation decreases that impact of maternal malnutrition," Charlton says.

While in clinical practice maternal malnutrition would be treated more simply by improving the diet of the mother, this approach of fetal supplementation may be valuable in other categories of intrauterine growth retardation. "We started with what was most likely to work," Charlton says. Now she and colleagues plan to investigate its application to more subtle causes of intrauterine growth retardation.

Most attempts at finding treatment strategies, however, await better answers to the questions of why and how the normal course of fetal development is changed to produce an abnormally small infant, and under what conditions that infant suffers adverse consequences.

"We may not need to prevent IUGR [intrauterine growth retardation] in the global sense," Sparks said during a discussion at the meeting. "Making the fetus bigger is not the goal. Morbidity is what you want to prevent."

Rosenfeld suggests that under some conditions being small might even be an advantage. "It may be a mode of adaptation to a bad environment [such as a hypertensive mother]," he says. William Oh of Brown University in Providence, R.I., agrees that ideally it would be useful to divide small-for-gestational-age babies into two categories for comparison; those that are impaired in some way and those that are not. Then researchers could search for differences in the histories.

The scientists agree that it will take a very large epidemiological study, following children for at least 2 to 6 years, to answer many of the pressing questions, such as whether late onset growth retardation has a detrimental effect. They say recent obstetrical practice has changed so dramatically (for instance more early induction of labor and better prevention of oxygen deprivation) that data collected in the 1960s is no longer relevant.

More information is needed on many fronts, from epidemiological, clinical and animal work, before physicians will know which pregnant women to suspect of growth retardation, how to diagnose it, whether it is likely to be detrimental to the child and finally what treatments can be applied. □