The Littlest Babies

Growth retardation in the womb, usually of unknown cause, affects millions of babies

". . . few medical men have a very clear conception of the progress of events during antenatal life. The drama of embryonic and fetal development and growth is, so to speak, going on, but the curtain has not been rung up, and the spectators get only confused impressions from the swaying of the drop-scene and from vague sounds, excursions and alarms, coming from behind it; yet no one doubts the existence of great activity post cortinam theatri, *and some from superior knowledge can judge how preparations are progressing . . ."*

—John W. Ballantyne, *Manual of Antenatal Pathology and Hygiene–The Fetus,* 1902.

By JULIE ANN MILLER

First of two articles

When the curtain finally rises on the drama of fetal development, the newborn is center stage. Is it a plump and robust baby or is it tiny and fragile? Each year approximately 16 million babies are born abnormally small because their growth was retarded in the womb. These infants, in general, run higher than normal risks of health problems at and after birth. In the United States, intrauterine growth retardation occurs in about 5 percent of all pregnancies and increases the risk of death for fetuses late in pregnancy and for newborns approximately five-fold. Medical investigators are puzzling over how to predict, detect and treat these "small-for-gestational-age" babies.

While there may be similarities in appearance between premature and growth-retarded small newborns, the small-for-gestational-age infant has some distinctive features. "These infants often have a wasted, malnourished appearance, yet the infants look alert and frequently appear older than their weights would indicate," says Joseph B. Warshaw of the University of Texas Health Science Center in Dallas. The growth-retarded fetus may have a smaller energy reserve than a normal fetus, and thus be less well-equipped to withstand stress before and during birth. The incidence of oxygen deprivation around the time of birth is greater, and many of the complications of growth retardation stem from asphyxia during labor and delivery, Warshaw says.

In theory the best definition of a small-for-gestational-age baby is one whose size is less than its genetic potential. But in practice, where genetic potential is impossible to define, babies with intrauterine growth retardation are identified by their size at birth. One common cutoff point for low birth weight is 2,500 grams or 5 pounds, 8 ounces, for a fullterm newborn, and correspondingly less if the baby is premature. Often investigators take into account differences in newborn size between populations and define as small for gestational age the 3, 5 or 10 percent of the fullterm infants lowest in weight.

Only in the last 10 years have studies of small newborns consistently distinguished between infants that are small because they are born prematurely and those that are small due to retarded growth in the womb. In the United States about 4 percent of live newborns are premature, while about 5 percent are considered small for their gestational age, says Donald McNellis of the National Institute of Child Health and Human Development, in Bethesda, Md. Some babies, of course, are both early and small for their gestational age.

While the percentage of premature babies in the newborn population varies relatively little around the world, the incidence of small-for-gestational-age babies is up to six times higher in developing countries compared to more economically developed areas. In both the United States and Cuba, recent declines in the overall incidence of low-weight births reflect a far greater decrease in small-for-gestational-age infants than in preterm babies.

Currently at least half the small-for-gestational-age babies are born from pregnancies during which there was no reason to suspect any problems, Robert J. Sokol of Wayne State School of Medicine in Detroit told a recent research planning workshop on intrauterine growth retardation held by the National Institute of Child Health and Human Development. Known causes of retarded prenatal growth include such genetic characteristics of the fetus as dwarfism, brittle bone disease and chromosome abnormalities. But more often it is maternal genetics and environment that limit prenatal growth.

Certain aspects of the medical history and clinical examinations of a pregnant woman are associated with an increased risk of having a growth-retarded baby. These factors include small size, relative youth (or the pregnancy being the first), malnutrition, smoking, certain diseases and a previous low-birth-weight child. In addition, blacks have a higher risk than whites of having a small-for-gestational-age baby and twins generally have lower birthweights than babies of singleton pregnancies.

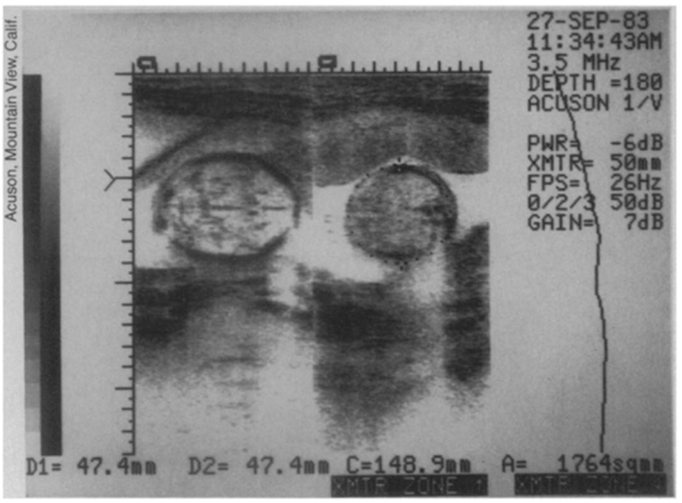
Since so many cases of intrauterine growth retardation escape prenatal detection, scientists have tried to set up screening procedures to identify high risk pregnancies. Several researchers now report that standard obstetrical observations and maternal history are not sufficient to reliably predict the birth of a small-for-gestational-age baby.

Sokol, for example, considered 100 risk factors available to a clinician before the 34th week of a pregnancy. With a computer, he analyzed the records of 5,414 pregnancies delivered at fullterm. He found eight characteristics that independently increased (by factors of 1.6 to 2.4) the risk of having a small-for-gestational-age baby. A woman having all eight factors had a 16-fold higher risk than a woman with none of the factors.

But the predictive value of this combined risk assessment was unimpressive. Among the pregnant women with the highest risk, less than half delivered a small-for-gestational-age baby. And 45 percent of the small newborns were born to women assessed at no more than average risk. "Thus nearly one-half of the pregnancies complicated by intrauterine growth retardation could not possibly be identified on the basis of the clinical risks in this rule," Sokol says. Researchers are now trying to improve on these attempts by adding the results of certain laboratory tests (such as a maternal glucose tolerance test) to the data included in the screening procedure.

When intrauterine growth retardation is suspected in an individual pregnancy, how can it be convincingly diagnosed? The greatest advance in detecting fetal growth retardation is the use of ultrasound (SN: 6/12/82, p. 396). This direct visualization of the fetus allows measurement of various body parts at different times in pregnancy and comparison to standard growth rates. Head and abdominal diameters, head-to-body ratio, femur length, total intrauterine volume and amniotic fluid volume have all been used in different studies of fetal growth retardation. But it may take a combination of two or more measurements to give a satisfactory prenatal evaluation.

"No one ultrasound measurement of the fetus has been shown to be totally accurate in detecting intrauterine growth retardation," says John T. Queehan and Gregory D. O'Brien of Georgetown University Hospital in Washington, D.C. "It is believed that the ability to define in-



Intrauterine growth retardation sometimes can be detected by the ratio of the circumferences of the fetal head (left) and the abdomen (right). In these high-resolution ultrasound images of a normal 20-week-old fetus, the cross-section of the head is taken above the ears and the abdominal image is at the level of the umbilical cord.

trauterine growth retardation should be improved with a three-dimensional image of the fetus with the use of femur length and circumference measurements." Other scientists have devised formulas using fetal head and abdomen circumferences or abdomen and thigh circumferences and femur length to predict birthweight of small babies.

Even newer imaging techniques are being considered for the evaluation of prenatal growth. Jack S. Cohen of the National Institutes of Health in Bethesda, Md., suggests that nuclear magnetic resonance (NMR) will prove useful in diagnosing intrauterine growth retardation. In a preliminary study in Scotland, Francis W. Smith, A.H. Adam and W.D.P. Phillips of the Aberdeen Royal Infirmary and University of Aberdeen used the technique to visualize 12- to 20-week-old fetuses of women scheduled for abortion. Head measurements and observations of the placenta were comparable to results of ultrasound. "The fetal detail displayed by NMR is greater than that seen by ultrasound and ... should provide a new method of tissue analysis and improve our knowledge of fetal development and growth," they say.

Although NMR imaging has been in clinical use for more than two years, there are not yet enough data on its safety to advocate use in pregnancy. Smith and colleagues say, "Nevertheless, we believe that it will prove to be safe and that the absence of ionizing radiation, the superior tissue definition compared with ultrasound and the ability to study tissue water will give it wide application in obstetric practice."

The measurement, in the maternal blood, of fetal or placental hormones provides a biochemical approach to the detection of prenatal growth retardation. Other tests challenge the placenta's capacity to synthesize, transport or metabolize hormones. Still others measure substances in the amniotic fluid.

Along with biochemical tests, measures of fetal activity and heart rate (called biophysical tests) are used to assess how the fetus is doing. When such measurements suggest the fetus is in distress, obstetricians hasten to deliver the baby.

While many biochemical and biophysical tests are in clinical use, their value as determined experimentally is controversial. Some find them "invaluable," while others are skeptical.

"All these studies [evaluating the biochemical tests] are deficient in that most of them are retrospective; they deal with small numbers of patients; they were performed only in large medical centers; their laboratory quality is often questionable and the definition of intrauterine growth retardation and the outcome of the newborn is often not mentioned," says Dan Tulchinsky of Brigham Women's Hospital in Boston. "Nevertheless, it appears that the sensitivity of any of the screening tests and their predictive value does not exceed 50 percent. It is also apparent that the number of publications on the monitoring of patients with hormone measurements has recently declined and that they have lost some of their previous popularity."

What are the consequences of being small at birth for the babies who survive the newborn period? Some of the babies are fine, while others experience problems. Most long-term studies report persisting growth lags. Although many small-for-gestational-age babies show an accelerated growth in the first year after birth, they generally remain smaller than their peers.

The effect of intrauterine growth retardation on nervous system development is more controversial. Some investigators report no problems; some find minor nervous system problems, including learning difficulties; others report a high incidence of major defects.

These divergent findings may be the result of loose and inconsistent criteria for intrauterine growth retardation and different durations of follow-up in the studies. Minor nervous system defects, such as poor motor coordination and learning problems, are difficult to identify until the child is at least six years old. But long-term studies run into difficulty ascribing minor deficits in school-age children to prenatal conditions, rather than to their lengthier postnatal experience. For example, some scientists find economic status plays a larger role than birth weight in determining intellectual development.

While everyone agrees that some babies are abnormally small, there is disagreement over how small-for-gestational-age should be defined in designing studies of its effects. Even if there were no intrauterine growth retardation, some babies would be smaller than others due to their own genetic makeup. Thus if small-for-gestational-age infants are defined, as is commonly done, as the smallest 10 (or 5 or 3) percent of the newborn population of a certain gestational age, the group will include some normal, but genetically small, infants. (There are difficulties in many cases reliably determining the exact gestational age of a fetus.) With this approach, some researchers argue it is better to take the 3-percentile group, so as to have less "contamination" with normal, genetically small babies. Other investigators believe only the larger (smallest-10-percent) group adequately represents the most common forms of intrauterine growth retardation.

Consideration should be given to the infant's growth potential by comparing the baby to any siblings and by taking into ac-

Smith, Univ. of Aberdeen

A new medical technique, nuclear magnetic resonance spectroscopy (NMR), someday may provide valuable information on prenatal growth. In this NMR image of a 12-week-old fetus, the umbilical cord, placenta and uterus are also visible.

count any ultrasound measurements that indicate diminished growth rate and the amount of fat and muscle in the newborn, says Rudy E. Sabbagha of Northwestern University Medical School in Chicago. But these considerations are more difficult to make and evaluate than a simple weight-for-gestational-age cutoff point.

To gain insight into prenatal growth retardation, it may be necessary to make divisions among low birth weight infants. According to Zena Stein of Columbia University in New York, comparing newborns of the same birth weight and gestational age, girls have a better survial rate than boys, blacks do better than whites, and twins and triplets do better than singleton births.

While some aspects of childhood development may simply reflect intrauterine growth retardation of any origin, the cause and severity of the retardation is thought to affect the longterm outcome. Chromosomal abnormalities in the fetus, chronic maternal disease, malnutrition and twinning, for example, are likely to affect different aspects of fetal growth and consequently have different influences on a child's development.

"Simple exclusion of genetic disorders and chronic intrauterine infections does not result in a homogeneous sample," says Pamela Fitzhardinge of the University of Toronto. "Studies are needed that identify fetal insult of a specific type occurring at a documented stage of fetal development."

In most cases it is not now possible to identify the cause of the retarded growth. Some investigators have begun to categorize growth retarded newborns and study the resulting groups separately. One rough division of small-for-gestational-age babies now being used is based on the relationship between their birth weight and length (and sometimes head circumference). This measurement ratio is thought to reflect when in pregnancy the retardation began.

If growth was diminished early in the pregnancy, both weight and length are decreased, resulting in a proportionately affected, or symmetrical, infant. But if, as is the more common case, the retardation occurred late in the pregnancy, after the period of most bone growth but before the final production of fat, the infant displays a greater deficit in weight than in length or head size, and is said to have had asymmetric intrauterine growth retardation.

Studies in England and Guatemala indicate that certain characteristics of children correlate with this division of intrauterine growth retardation. Those who had experienced the symmetrical form, remained lightest and shortest at three years of age They also had the smallest head circumferences and the lowest mental development. In contrast, those who had experienced asymmetric intrauterine growth retardation showed greater catch-up growth just after birth and had mental development intermediate between the symmetrical subjects and normal controls.

"Therefore it can be concluded that the physical growth and mental development of intrauterine growth retardation [children] are associated with their characteristics at birth, and that they are similar regardless of the ethnic background and postnatal environmental conditions of the ... population," Jose Villar of Johns Hopkins University says.

A study using a more specific categorization examined infants whose heads had been measured with ultrasound during the pregnancy. David Harvey of Queen Charlotte's Maternity Hospital in London demonstrated that children who had had significant deceleration in head growth before 26 weeks of gestation score lower on cognitive (thinking) tests than do other children.

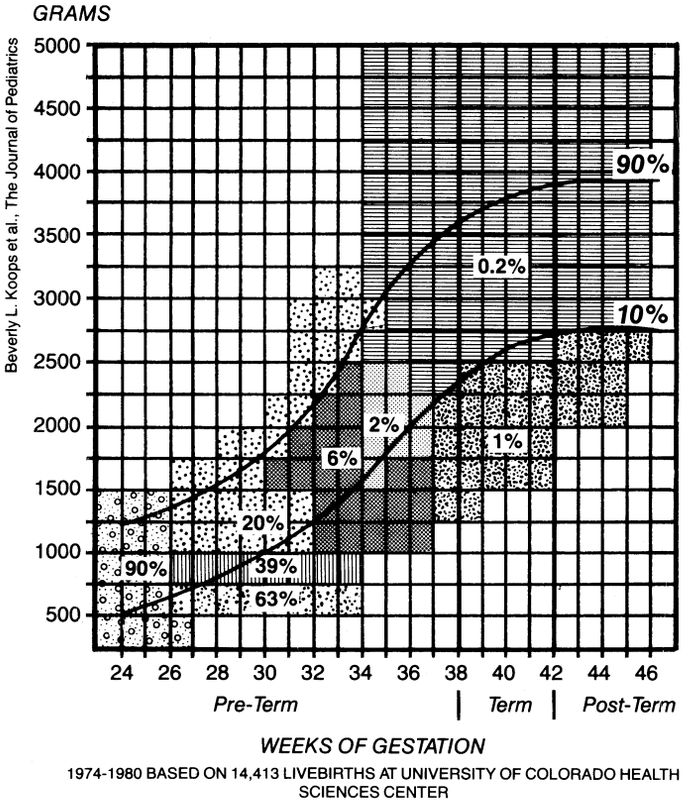
Hypertensive disorders are commonly found among mothers of small-for-gestational-age infants. These babies often have "brain sparing" development — the fetal head growth is affected less than other body parameters. Eve K. Winer and Nergesh A. Tejani of Nassau County Medical Center in New York report that these children did better in tests of intellectual development given at 4 to 7 years than did the other small-for-gestational-age children, where the growth retardation was of unknown cause.

Head circumference at birth is more important than weight and gestational age in predicting infant development, report Evelyn Lipper and colleagues at Albert Einstein College of Medicine in New York. Infants with smaller than normal head circumference for their gestational age were more likely to have low scores on a development test and to have severe neurologic deficits at seven months of age than were small-for-gestational-age (and normal) infants with appropriate head circumference. "These observations suggest that head circumference at birth may be the single most important variable for subsequent neurobehavioral outcome," the investigators suggest.

Options for treating a fetus suspected of growth retardation are currently very limited. When the cause is maternal disease, the illness is treated however possible. Bed rest is often prescribed for the pregnant woman with a growth-retarded fetus. Late in pregnancy, obstetricians may induce early delivery if they believe the baby will do better in the intensive-care nursery than in the womb. In any case, the birth of a baby suspected of intrauterine growth retardation is monitored intensively.

To develop more powerful treatments of intrauterine growth retardation, scientists must know more about why and how the growth retardation takes place. Warshaw says, "Only through multidisciplinary approaches ranging from studies of population influences to biological investigations of regulation of cell growth will continued progress be made in eliminating this most serious and important developmental defect of low birthweight." □

Neonatal Mortality Risk by Birthweight and Gestational Age



1974-1980 BASED ON 14,413 LIVEBIRTHS AT UNIVERSITY OF COLORADO HEALTH SCIENCES CENTER

Beverly L. Koops et al., The Journal of Pediatrics

Both gestational age and weight at birth contribute to an infant's risk of dying soon after birth. At each gestational age beyond 26 weeks, a baby of appropriate weight (plotted here between the curves representing the 10th and 90th percentiles of birthweight) has a lower mortality risk than an abnormally small infant. Risks of dying in the first four weeks after birth are presented as the numbers in the centers of the shaded zones.