

Academic Advance

Coming of age: Fetus as patient

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SCIENCE HAS COME A LONG WAY SINCE FRENCH PHILOSOPHER JEAN-JACQUES ROUSSEAU REFERRED TO THE FETUS AS A "WITLESS TADPOLE" SOME 200 YEARS AGO. IN FACT, FAR FROM BEING VIEWED AS WITLESS. THE FETUS IS NOW THE SUBJECT OF INTENSE STUDY BY PRENATAL PSYCHOLOGISTS WHO SAY THAT THERE IS UNQUESTIONABLY INTELLIGENCE BEFORE BIRTH. WHILE MANY OF THESE PSYCHOLOGISTS ARE STILL FRINGE DWELLERS IN THE FIELD OF FETAL MEDICINE A SCIENTIFIC MAINSTREAM IS PENETRATING THE WORLD OF THE WOMB LIKE NEVER BEFORE. USING STATE-OF-THE-ART TECHNOLOGY TO SHED LIGHT ON THE BEHAVIOR OF THIS PREVIOUSLY SHADOWY BEING AND AS A RESULT, SAY OBSTETRICIANS AND PERINATOLOGISTS, IT IS NO LONGER ONLY THE MOTHER THAT THEY CONSIDER THEIR PATIENT, BUT THE FETUS AS WELL.

Ushering in the age of fetal medicine is highly sensitive ultrasound and Doppler technology that lets physicians study the fetus in detail, from its anatomy and behavior to its neurology and psychology. This plethora of information being obtained by physicians at the University of Michigan Medical Center and elsewhere is providing a comprehensive measure of "normal" growth and development that can be used to diagnose fetal abnormalities as early as 10 weeks. This new

knowledge has spawned a host of interventional (and sometimes controversial) therapies, from fetal blood transfusions to intrauterine surgery, which would have been unthinkable two decades ago.

"For years obstetricians were just doctors who pulled babies out," says Timothy R.B. Johnson, M.D., professor and chairman of the Department of Obstetrics and Gynecology. "The exciting thing is that now we're having to learn things we never had to know. We're having to become pediatricians, neurologists and developmental psychologists because suddenly we have access to the fetus as a patient."

Johnson, who recently came to the U-M from Johns Hopkins, is a national leader in the study of fetal behavior. During the last several years he has done unique research on the interrelationship of fetal heart rate and movement using an innovative machine base on Doppler technology. Although the machine is becoming widely available in the United States, Johnson is among the few physicians to have used it for fetal behavior research.

"We took tools that were being applied to newborns and said, "OK, we have ultrasound and all this technology and now we can start doing a physical examination, a neurobehavioral exam and an Apgar score on the fetus," he says. (An Apgar score is a system used to assess the condition of a newborn. Five factors, including respiration, heart rate and muscle tone, are rated from 0 to 2; a score of 7 to 10 indicates a well baby.)

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As the study of fetal behavior has developed, it has been governed by the view that the transition from fetus to baby is a continuum rather than an abrupt transformation brought about by the birth event. What the fetus does at six weeks prior to birth, according to this view, is nearly identical to what it does six weeks after; consequently, there's growing consensus among physicians that the late term fetus and the newborn should be treated equally.

While electronic monitoring is now the norm in hospitals for gauging the fetal heart rate, this approach alone is often not enough to indicate distress and abnormalities inside the womb. What is more reliable, Johnson says, is studying the relationship between fetal heart rate and movement. With his Doppler transducer, which consists of a belt strapped around the mother's abdomen that identifies and records fetal heart rate and movement, Johnson can monitor how a fetus integrates its activities; whether or not the heart rate goes up when the fetus sucks its thumb, for example. Johnson also can look at how a fetus organizes its awake/sleep cycles. By monitoring these interrelationships, he can get a more reliable indicator of the health of the unborn child and perhaps predict outcomes for those with abnormalities.

"We are in the process of describing normal fetal development so we can look at a fetus with, say, hydrocephalus and see if it's developing normally in utero. Hopefully, this will help us predict how it will do after birth," Johnson says. If physicians notice that a fetus is not developing normal

behavior that the heart rate does not increase when it moves they may take this as an indication of trouble.

"Until now, often the only way to tell how a baby born with birth defects would do was to watch him for the first two years and see how he developed. Suddenly we have this window on the fetus that allows us to look at how it's developing in utero at a time when it changes very, very quickly," Johnson says.

With their new tools, obstetricians can chart the developmental milestones of fetal behavior just as pediatricians do for a newborn. Detectable movement, including hiccups, begins around the eighth week of gestation; the first hand-face contact occurs between 10 and 11 weeks, as does stretching and discernible breathing. Yawning begins between 11 and 12 weeks, and sucking and swallowing around 13 weeks.

"Babies are practicing in utero all the things they need later," says Johnson. "It's as if they are exercising for a track meet."

"Johnson and his colleagues have learned that sick fetuses are like sick babies in that the behaviors they acquire last the higher functions are the first to go. For example, a fetus can be profoundly neurologically impaired and still hiccup.

DO FETUSES DOZE DURING BIRTH?

Another aspect of fetal behavior that Johnson has been particularly interested in is the role of the fetus during labor. The conventional wisdom used to be that babies went to sleep during birth, he says, but this was mainly because it was impossible to accurately study them in the process. With his Doppler machine, however, Johnson has found that not only do babies move throughout labor, but they are particularly active during contractions, perhaps even stimulating some of them by kicking the mother's uterus.

Though he is continuing his research monitoring healthy pregnant women. Johnson says the greatest clinical application of fetal behavior monitoring is for those with high-risk pregnancies. In addition to diagnosing abnormalities, doctors can use such data to

help counsel parents to make the best decisions for themselves and their unborn child.

In utero diagnoses are being made earlier than ever before, in some cases as early as 10 weeks. One new technique that achieves this is chorionic villus sampling, in which a bit of the placenta is extracted using a small, malleable catheter that is inserted through the cervix or uterine wall. It provides physicians with almost the same information as an amniocentesis, but six weeks earlier. Another technique, still considered experimental, is embryofetoscopy, in which a fiber optic scope smaller than a needle in diameter is threaded into the uterus to allow physicians to visualize the fetus as early as six weeks after conception.

But does all this early information guarantee better outcomes? The answer, says Johnson, is often no. For example, the diagnosis of diaphragmatic hernia can now be made in utero; those with even the severest hernias can now be saved at birth. But while the sickest babies may be surviving, says Johnson, their long-term prognosis may be worse.

"Now we are identifying prenatally those babies who have very bad disease, who five or 10 years ago might never have made it out of the delivery room," says Johnson. "Now we can make the diagnosis of diaphragmatic hernia at 19 weeks, and the counseling for the parents will be different."

The question remains, though, what are the alternatives once a Doppler transducer or a high resolution, real-time ultrasound has revealed a defect? Spina bifida, renal cysts, hydrocephalus, diaphragmatic hernias, cleft lips and missing digits are among the abnormalities that are now detectable during routine ultrasounds. For most expectant parents the options are to watch, wait or terminated. But in a few cases, interventional therapies can make a difference.

BEYOND DIAGNOSIS

"We were taught in medical school that if you got near the umbilical cord with

a needle, lightning would strike," says Clark E. Nugent, M.D., clinical associate professor of obstetrics and gynecology. "But now, guided by ultrasound we can not only take things out, we can also put them back in."

What Nugent is referring to is PUBS, or percutaneous umbilical blood sampling, a procedure that began in the late 1980s in France to diagnose fetuses with toxoplasmosis, a disease that's endemic among the French due to their fondness for raw meat. In Michigan, U-M physicians were among the first to offer the technique, which consists of passing a needle through the uterine wall and into the umbilical cord to do fetal blood monitoring and transfusions.

Typically, fetal blood transfusions are used to reverse severe anemia, which can be caused by such conditions as Rh incompatibility or parvovirus B19 (also known as fifth disease). Because parvovirus, which causes cheek rashes, can reach epidemic proportions among school-aged children, pregnant women easily can be exposed to it. And while half of these women have an immunity to the virus, the 10 percent who develop the disease put their fetus at risk.

"The virus sets up shop in the fetal bone marrow and diverts it for its own purpose," says Nugent. "The fetus quits making its own blood cells and becomes severely anemic."

If the mother doesn't know she's been exposed to the virus, behavioral indicators of the anemia in utero can provide a clue: The fetus slows down and becomes lethargic. While some fetuses recover from the virus on their own, others need a blood transfusion to survive; otherwise they'd die in the womb from massive edema and heart failure.

To perform a transfusion, Nugent teams up with a radiologist who guides him to the umbilical cord with ultrasound. Nugent first gives the mother a muscle relaxer to calm the fetus so it doesn't kick the needle.

The earliest age at which the therapy is done is 18 weeks, and there is a 1-percent chance of miscarriage. But providing the condition is caught in time, the infant will recover fully after the transfusion.

Drugs also can be injected directly into the fetus through the umbilical cord. One such therapy involves the injection of medication to treat fetal arrhythmia. But so far this method has proven ineffective and in some cases fatal to the fetus. The reason for this, says Nugent, is that unlike blood cells injected into the fetus directly, drugs will cross the placenta and become diluted, so it is difficult to establish an optimum dosage. To maintain a stable concentration, the mother has to be medicated at the same time.

What may prove effective down the road, however, is using the umbilical cord as

a gateway for fetal gene therapy. "The fetus should be an ideal candidate for stem-cell transplantation because it is immunotolerant, you will not have the same problem with rejection that you will have in a newborn," Nugent says.

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