What Determines the Timing of Birth?

Why newborns arrive on their own schedule—not yours

by Kathryn Sergeant Brown, *special correspondent*

Babies arrive unannounced. Some show up three weeks early. Others appear 10 days past term. Their timing seems random—but it's not. Together the fetus and placenta establish the moment of childbirth by launching a chemical cascade that sets off a mother's contractions. The question is, How does this embryonic duo set the date?

Scientists are now pursuing two main scenarios. According to the first, the placenta runs on a nine-month clock, telling time by the flux of pregnancy hormones. Your clock may run fast, causing an early birth, or slow, bringing a late baby. According to the second, the fetal brain acts like a computer, logging its own growth or the environmental changes until the moment for birth is right. Exploring both ideas, researchers have found telltale hormonal changes that portend premature birth. By picking up on and manipulating these hormonal cues, doctors could one day prevent some babies from being born before their time.

One in 10 babies is born prematurely, which is defined as before the 37th week of pregnancy. Not yet fully developed, these tiny newborns can succumb to serious respiratory infections or to neurological problems such as cerebral palsy. Preterm birth is the leading cause of infant death in the U.S. What is more, because there is no reliable way to tell which women are likely to deliver prematurely, all doctors can do is closely watch women who have risk factors for early delivery. Such risk factors include having had a premature baby previously, abusing drugs or alcohol, smoking or harboring an untreated vaginal infection.

Scientists have studied birth timing for more than 60 years—mostly using sheep, whose brain biochemistry resembles our own. Several weeks before birth, the unborn lamb's brain begins a hormonal relay race. At the base of the brain, the hypothalamus fires off hormones to the nearby pituitary gland, which then sends a signal through the bloodstream to the fetus's adrenal glands, which are atop the kidneys. The adrenals, in turn, pump the hormone cortisol into the fetal lamb's bloodstream, where it flows to the placenta and activates the enzymes that make estrogen. And it is an estrogen surge that ultimately prompts the muscles of the uterus to contract, bringing lambs (and humans) into the world.

But some researchers suggest that—in humans, at least—this hormonal relay begins in the placenta, not in the baby's brain. The placenta thrives for nine months, after which its cells rapidly die off. Somehow, scientists reason, the placenta must be keeping time. "[Birth timing] is probably much like the onset of puberty and menopause," says Roger Smith of the University of Newcastle in Australia. "These are major biological events that are preprogrammed to occur at certain points." Smith suggests that heredity might determine whether a woman has a fast- or slow-running birth clock or one that runs on time. Preterm births sometimes run in families, he says.

How does the placental clock tell time? Possibly by following the flux of pregnancy hormones. One example is corticotropin-releasing hormone (CRH) produced by the placenta. CRH rises and falls in a woman's blood throughout pregnancy, peaking in the weeks before birth, when it causes estrogen to increase as well. Every pregnant woman appears to have a unique CRH pattern during pregnancy, suggesting a personal timetable.

In a study of 485 pregnant women, Smith and his colleagues found that blood levels of CRH during the first trimester could predict which women were destined for early, normal or late deliveries. Women with high CRH levels tended to have preterm births; those with low CRH levels often had postterm births.

If Smith's study is confirmed, doctors might one day check a pregnant woman's CRH level to learn whether she's likely to deliver prematurely. If her CRH levels are high, the physician might prescribe drugs to prolong pregnancy or prenatal corticosteroids to speed a fetus's lung development. In the future, Smith says, drugs specifically intended to lower CRH could possibly delay delivery as well.

In addition to CRH, estriol—a form of estrogen—also might be part of the placental clock. Biex, a biotechnology company in Dublin, Calif., is now developing an estriol-based test for premature delivery. Three weeks before childbirth, estriol levels in a pregnant woman's blood peak, explains James A. McGregor of the University of Colorado at Denver. He has worked with Biex to develop SalEst, a test that detects this estriol crest in a woman's saliva, which mirrors levels in the blood.

In clinical studies, SalEst—which has received preliminary Food and Drug Administration approval—correctly predicted 57 percent of preterm births. Women with known risk factors could take the test several times near the end of their pregnancies to see if they really were likely to deliver prematurely.

According to the second scenario, some researchers say the fetal brain carries the program for computing the proper birth time. Peter W. Nathanielsz of Cornell University—who supports this "fetal computer" theory—suggests that the fetal brain tracks the maturation of the baby's lungs, heart and other organs. When the baby is mature enough to live outside the womb, the fetal brain launches the hormonal cascade that leads to childbirth. "Scientists have tended to look for a single trigger that sets off the fetal hypothalamus and begins the process of childbirth," Nathanielsz says. "I think it's a much more complex process than that. Rather than following some clock, I think the fetus is evaluating the [maturation] of its body."

Putting a slight spin on the fetal-computer concept, Caroline McMillen of the University of Adelaide in Australia suggests that birth begins when a fetus's brain senses a drop in oxygen and glucose in the womb. Near the end of pregnancy, as the fetus grows, the nutrients it receives from the placenta become inadequate, McMillen says. The result, in short, is stress.

McMillen has found that levels of neuropeptide Y (NPY)—an appetite-stimulating hormone that surges in starved animals—skyrockets in the brains of fetal sheep during the last two months of gestation. The NPY boom jump-starts cortisol production by the fetal lamb's adrenal glands, prompting the hormonal frenzy that leads to birth. But McMillen concedes that proving the stress hypothesis will require a lot of research. Whether clock or computer, she says, the fetus-placenta duo clearly sets the timeline for childbirth. It's the first of many occasions when child—not parent—decides life's pace. SA