LENNART NILSSON From *Behold Man*

Searching for Preeclampsia's Cause

Researchers zero in on one of the most dangerous disorders of pregnancy

by Kathryn Sergeant Brown, *special correspondent*

Michelle Wemple had a picture-perfect pregnancy. She hiked. She ate well. She felt healthy and hopeful. So her 36th-week prenatal checkup came as a shock. For some reason, Wemple's blood pressure was soaring. A urine test also showed her kidneys were leaking protein. Her doctor suggested inducing labor—immediately. "How could things suddenly go so wrong?" Wemple asked. "I'd done everything I possibly could to be healthy. And I didn't feel sick." Yet Wemple—like one in 20 pregnant women—had preeclampsia.

Women with preeclampsia, which is also called toxemia of pregnancy, suddenly develop high blood pressure and begin to retain fluid and excrete vital proteins. If the baby isn't delivered quickly or the physician can't lower the woman's blood pressure using drugs, the condition can progress to full-blown eclampsia, which brings on deadly seizures.

Doctors do not know why some women develop preeclampsia—or how to respond, short of administering blood pressure drugs and delivering the baby as soon as possible, sometimes too early for it to live. But that could soon change. More than a dozen labs worldwide are now studying preeclampsia. Their findings could help doctors rate every pregnant woman's risk of the disorder. And although a specific therapy is still years away, researchers hope they might one day have more to offer women with preeclampsia than just a rushed delivery. "Our understanding of preeclampsia is quickly improving," says James M. Roberts, director of the Magee-Womens Research Institute in Pittsburgh. "We've moved further in the last few years than we have in the past 50."

During a normal pregnancy, mother and baby quickly form a tight biological bond. Early on, fetal cells form the placenta, a lifeline that ferries nutrients and oxygen from the mother's uterus down the umbilical cord to the baby. Some pioneer placental cells actually enter uterine blood vessels, elbow out the maternal cells lining the vessels and then stretch the vessels, enabling them to shuttle more blood as the fetus grows.

A four-month-old fetus is seen cocooned in the amniotic sac.

But in preeclampsia, scientists say, this cooperation falters. According to one scenario, too few placental cells enter uterine blood vessels—and those that do simply lie around, rather than flattening out and expanding the vessels. Alternatively, a mother's blood vessels might be stiff and resist expansion because of prior hypertension or diabetes. "Preeclampsia can come from either the fetal or maternal side," says Kenneth Ward of the University of Utah.

In either case, the result is a poorly developed placenta that spells trouble for both mother and child. The baby gets meager rations of oxygen and nutrients, and the mother's body senses damage to uterine blood vessels and reacts in a variety of ways. Her small arteries spasm, boosting blood pressure. Her blood vessels may leak water, causing rapid weight gain and swelling. Her level of platelets, specialized cells that clot blood, can plummet. Last, her kidneys may begin to fail, expelling vital proteins along with the usual metabolic waste.

Most women with preeclampsia develop a mild case late in pregnancy, when their baby can be delivered safely, as Wemple's ultimately was. But if a woman falls ill before the third trimester, her premature baby might not survive.

Deciding who is at risk for preeclampsia is tricky. The condition tends to run in families and to affect first-time mothers. Existing hypertension, diabetes or kidney disease raises a woman's susceptibility. Beyond these broad parameters, however, doctors are unable to predict which women will become sick. To define risk better, scientists are hunting for biochemical flags that warn of the possibility of preeclampsia.

Ward and his colleagues reported that women who inherit a variant of a gene encoding a common blood-clotting protein called factor V tend to form blood clots in their placentas, which could lead to preeclampsia. The researchers also found high rates of preeclampsia among women with an abnormal version of angiotensinogen, a protein that helps to control blood volume throughout the body and signals uterine blood vessels to expand during pregnancy. They are now analyzing the angiotensinogen-preeclampsia link among 24,000 women. If the connection pans out, it might yield a blood test to identify women at risk as early as their first prenatal checkup.

The placental cells themselves could also offer tools for predicting which pregnant women might be prone to preeclampsia. For example, Susan J. Fisher, Yan Zhou and their colleagues at the University of California at San Francisco are now analyzing the repertoire of proteins made by cells isolated from the placentas of women who had preeclampsia. Any placental proteins that occur in unusual amounts during preeclampsia might become diagnostic markers; however, a blood test based on such a protein would be years away.

Yet without a treatment or preventive for preeclampsia, knowing one's risk is only half the battle. A surefire preventive has been elusive. A handful of studies linked low-calcium diets to high preeclampsia rates in Latin America, suggesting that calcium supplements might prevent the disorder. But last year, a major study conducted by the National Institutes of Health found that calcium does not prevent preeclampsia in otherwise healthy women. Hopes also rose—and then fell—over aspirin, which is thought to relax blood vessels, thereby lowering blood pressure. Some scientists now suggest that antioxidants might prevent preeclampsia. But Richard J. Levine of the NIH, who headed the calcium study, is skeptical. "We need to know a lot more about this disease before we can block it," he says.

In fact, doctors might never cure a single disease called preeclampsia—because, like heart disease or cancer, the disorder could come in several varieties, supposes John T. Repke, chairman of obstetrics and gynecology at the University of Nebraska Medical Center. Just as breast and lung cancers are treated differently, preeclampsia caused by fetal cells or a mother's rigid blood vessels—or something as yet undiscovered—might warrant unique therapies. According to Repke, pinning down preeclampsia's cause in just a subset of women might prove easier than solving the entire puzzle. In the meantime, the best thing a woman can do is stick with prenatal checkups. SA

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

Just Say No—to Pain

Today there are better choices for pain relief during labor and delivery

by Denise Grady, *special correspondent*

When it comes to pain medication, women in labor are tough customers. They want to remain awake, alert and in control but free of pain—without side effects that might harm them or their babies.

A decade ago that wish list could not be fulfilled. Anything that gave the mother some relief, it seemed, threatened the baby or slowed labor, increasing the chances of a cesarean section. For instance, narcotics, such as a shot of Demerol, would ease a mother's pain but could interfere with the baby's breathing. Similarly, spinals and epidurals—in which physicians inject painkillers into the sac surrounding the spinal cord or into the epidural space just outside it—would numb the spinal nerves that transmit the pain of uterine contractions but could also make it hard to push. Indeed, women would often be too weak to get out of bed during labor. And spinals could also leave the mother with a ferocious headache caused by the leakage of spinal fluid from the needle puncture.

Although some women eschewed painkillers during labor because they wanted to experience natural childbirth, others wanted relief. But given the risks, many women felt obligated to forgo medication. Some women also succumbed to guilt: during the 1960s, 1970s and 1980s, the social pressure for natural childbirth became so intense that in some quarters there was a sense of shame or dishonor attached to asking for pain medication during labor.

Times have changed. "What anesthesiologists can now provide for pain relief is a lot closer to a natural delivery than it was 10 or 12 years ago," says Richard M. Smiley, director of obstetric anesthesiology at Columbia-Presbyterian Medical Center. "In the vast majority of cases, we're able to achieve 95 to 100 percent pain relief, and the woman is still relatively mobile and still has complete strength."

The trick lies not in a revolutionary new therapy but in combining familiar drugs in new ways for spinal and epidural anesthesia. In the past, doctors giving epidurals would inject a Novocain-like local anesthetic into the epidural space in a woman's spine and leave in the catheter so that additional medication could be injected later. The drug would numb everything below the waist but would also cause considerable weakness. "It was difficult to push," Smiley says, and the medication could sometimes interfere with contractions and impede labor.

Today doctors add small amounts of opioid drugs such as fentanyl to the epidural injection. Opioids ease pain without causing weakness and allow the dose of the Novocain-like drug to be reduced by up to 75 percent. Women remain strong and able to push, and Smiley says he has seen no convincing evidence that this type of anesthesia interferes with labor, although there is still some debate about whether it does.

With the new epidural technique, women may still feel some discomfort and pressure, Smiley notes, but little pain. The technique is most effective during the first stage of labor, which is considered the most painful. The uterine contractions and dilation of the cervix that occur during the first stage produce a visceral type of pain that is particularly hard to tolerate. Most women find it easier to endure the pain of the second stage of labor, in which they deliver the baby through the birth canal.

"Almost all progressive obstetric anesthesiologists now combine locals with opioids," Smiley states. But this method of treatment requires more time and attention from the doctor, who needs to check on the patient every hour or so to make sure her pain is still under control.

Spinal anesthesia is also used more today than it was in the past, according to Smiley, because redesigned needles have greatly reduced the leakage of spinal fluid that causes headaches. Whereas epidurals take about 10 minutes to work, pain relief with a spinal containing either opioids or opioids plus a local anesthetic is almost instantaneous. "The pain relief is so fast that patients love you immediately," he says. The main drawback of a spinal injection is that the pain relief may last only a few hours. In contrast, an epidural can provide continuous relief for as long as the catheter is left in.

"Most of our patients really like the spinal," Smiley observes. "Labor nurses want it for themselves." Some physicians will give a woman a second spinal if she requests it; others prefer not to puncture a woman's spinal membranes twice.

Sheila Goodman, an obstetrician at Fairview University Medical Center in Minneapolis, has also found that women in labor prefer spinal injections. She adds that she herself has tried both spinal and traditional epidural anesthetics for the birth of her own children and that she much preferred the spinal.

Some doctors have been experimenting with a procedure in which they combine low doses of spinal and epidural anesthesia, so that a laboring woman gets both immediate pain relief from the spinal and lasting pain control from the epidural, while retaining her ability to walk. With the combination, "patient satisfaction is superb," according to Michael Nageotte, an obstetrician at Long Beach Memorial Medical Center in California and the lead author of a paper in the *New England Journal of Medicine* last December describing the procedure.

In a study of 761 women giving birth for the first time, Nageotte and his colleagues found that those who had the combined spinal-epidural anesthesia were less likely than those who had epidurals alone to need forceps to help with delivery. But the study also suggested that the odds of needing a cesarean increased if either type of anesthesia was given too early in labor, before the cervix had dilated to four centimeters or more and the baby had descended well into the birth canal.

As for effects on the fetus, Smiley asserts that with the low doses of medication used today, very little of the spinal or epidural injections reach the baby. "It's almost a nonproblem," he says. Epidurals do have the potential to lower the mother's blood pressure and harm the baby by reducing blood flow to the placenta, but Smiley observes that adverse effects from that are very unlikely.

Traditionally, the greatest wariness over the use of painkillers during labor has come from childbirth educators, who tend to advocate natural childbirth and to express concern that medication increases the likelihood of a forceps delivery or a cesarean section. But some counselors now recognize the benefits of anesthesia for women who want it, according to Smiley. "Patients have gone back to [their childbirth educators] and said, 'What [the anesthesiologist] did allowed me to push, and it was a good experience.'"