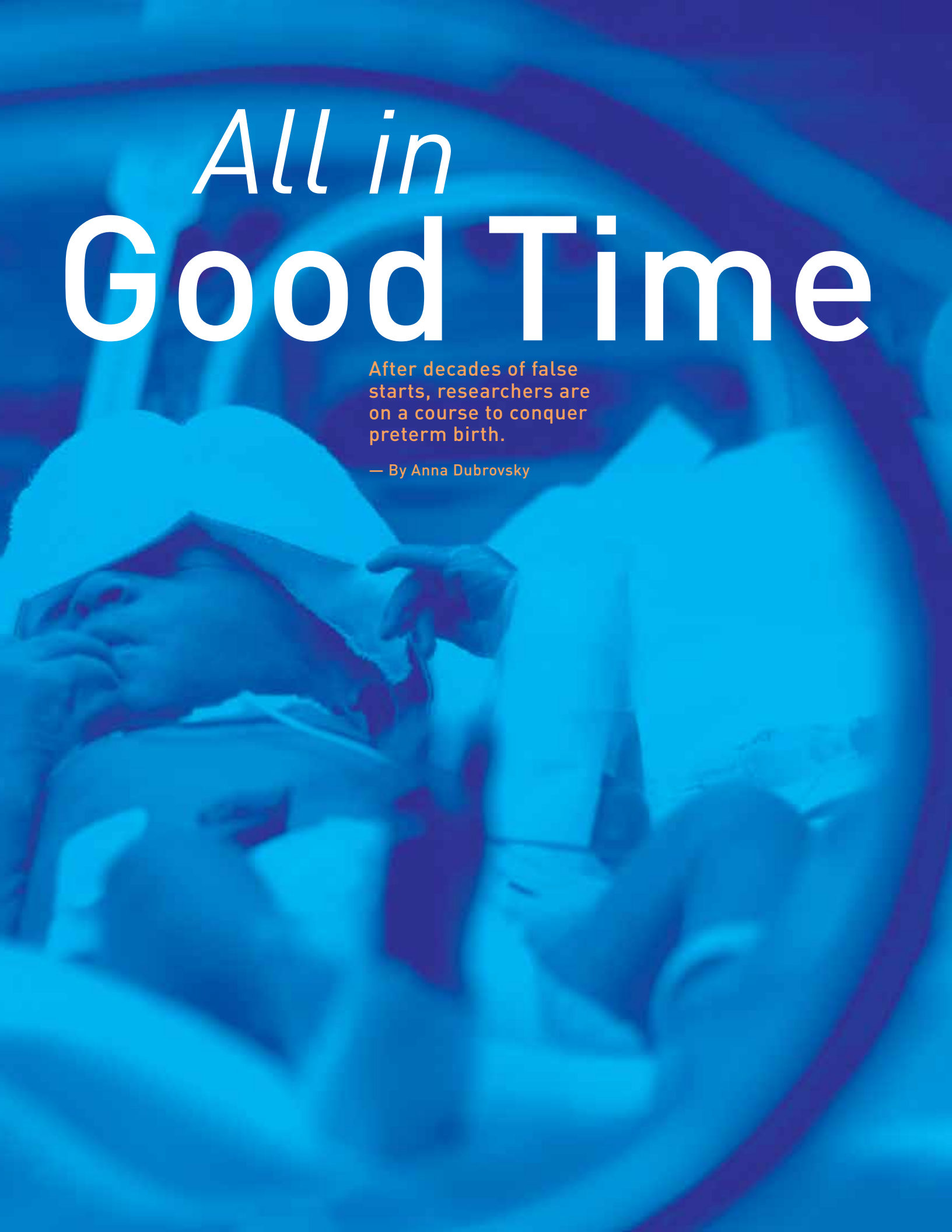

All in Good Time

After decades of false starts, researchers are on a course to conquer preterm birth.

— By Anna Dubrovsky

As the regional referral center for high-risk pregnancies and an otherwise popular place to give birth, Magee-Womens Hospital of UPMC boasts the largest neonatal intensive care unit (NICU) in Pennsylvania. More than 1,000 seriously or critically ill newborns are treated there each year.

Hyagriv Simhan, MD, chief of the Division of Maternal Fetal-Medicine, would like nothing better than to render it useless. "Magee's NICU does a great job," he says. "But my job is to put it out of business."

Dr. Simhan is devoted to solving the riddle of preterm birth, a leading cause of infant death, illness, and disability. Each year in the United States, more than half a million babies are born before reaching full term, or 37 weeks of gestation. The odds of giving birth prematurely are 1 in 8 — about the same as a woman's lifetime risk of invasive breast cancer.

Like cancer care, prematurity care has come a long way in recent decades. Thanks to NICUs like Magee's, the vast majority of preterm births aren't death sentences. In 1963, the youngest child of President John F. Kennedy and First Lady Jacqueline Kennedy was born about five weeks early and died of respiratory failure two days later. Had he been born today, the technologies of the NICU almost certainly would have saved his life.

That's the good news. Here's the bad: While mortality in premature infants has fallen sharply, the rate of preterm births in the United States has not. In fact, it rose by more than one-third from 1981 to 2006, when it began a modest decline attributed to a new hormonal treatment for women with a history of preterm delivery. Researchers and doctors are still struggling to understand what causes women to give birth prematurely. "We haven't found a smoking gun," says Steve Caritis, MD, who preceded Dr. Simhan as chief of maternal-fetal medicine and has been studying prematurity since the mid-1970s. Consequently, they can't predict which women will deliver prematurely.

You wouldn't blame them for throwing in the towel. Instead, Drs. Simhan and Caritis and scientists at Magee-Womens Research Institute (MWRI) have a decidedly sunny outlook. "The skeptic may say, 'Jeez, you guys haven't done anything over the last 40 years,' but I think we're closer now than we've ever been," Dr. Caritis says. "We have a better understanding of preterm birth than ever before. We never had a medication or treatment that actually reduced prematurity rates and improved perinatal outcome, but now with progesterone supplementation, we have a treatment that has proven effective in reducing preterm delivery in certain high-risk women. So our understanding of preterm birth and its causes and treatments is increasing fairly rapidly, and with molecular techniques, it will get even faster."

Magee is uniquely poised to make the next breakthroughs. "We have experts in many key areas of prematurity," Dr. Caritis says. "There are very few places in the country that have this many investigators focusing on prematurity." In addition to Drs. Caritis and Simhan, who are internationally recognized experts on labor-inhibiting drugs, the team includes Jennifer Condon-Jeyasuria, PhD, whose lab has identified a cellular protein that appears to keep the uterus from contracting, and Lisa Bodnar, PhD, MPH, RD, whose research focuses on the impact of maternal nutrition on birth outcomes.

Each year, there are more than half a million preterm births in the United States and more than half a million preterm-related deaths in the world.

The volume of births at Magee and its experience in grand-scale scientific studies also distinguishes it from other institutions, says Dr. Simhan. "We are unique because we have this tradition of being able to do clinical and biological research in large groups of women. The fact that we can extend that research to the newborn and infant period and beyond is truly unparalleled, and what we discover will help prevent the consequences of prematurity for children all over the world."

The Progesterone Puzzle

The year 2003 marked a watershed in the war against preterm birth. A multicenter research network that included Magee released the results of a clinical trial on the effects of a drug called 17 alpha-hydroxyprogesterone caproate (17-OHPC) on pregnant women with a history of spontaneous preterm delivery. The researchers found that weekly injections of the naturally occurring hormone reduced preterm birth by 34 percent. And infants of women treated with 17-OHPC had significantly lower rates of several complications associated with prematurity. In response, the American College of Obstetricians and Gynecologists endorsed the use of 17-OHPC to prevent recurrent preterm delivery. After decades of research and failed treatments, ob-gyns finally had a proven prevention strategy.

Separate trials have shown that administering progesterone by vaginal suppository greatly reduces the rate of preterm deliveries in women with a short cervix.

"We know progesterone supplementation works, but we don't know why it works," says Dr. Caritis, who helped lead the groundbreaking study on 17-OHPC injections. He's now intent on answering that question. Understanding how progesterone levels affect the timing of labor could lead to further treatments for preterm birth.

Dr. Condon-Jeyasuria may have found part of the answer. Her research suggests that progesterone regulates a cellular protein called caspase-3, which robs uterine muscle cells of their ability to contract. Caspase-3 levels in the uterus soar in the earlier months of pregnancy and taper off in the later months. When the protein disappears, the muscle cells regain their ability to contract, setting up the conditions for labor. "Nobody had looked at caspase-3 and its effect on the uterus," says Dr. Condon-Jeyasuria, whose trailblazing was rewarded with a $475,000 grant from the March of Dimes and a five-year $1.5 million grant from the National Institutes of Health.

She believes her lab's unorthodox approach to the study of preterm birth helped it snag the sizeable awards. "A lot of researchers are trying to identify the silver bullet that causes the uterus to suddenly contract. We've taken a different tack: Why doesn't the uterus contract all the time? Why doesn't preterm birth happen more often? Why is it only 1 in 8 pregnancies? There has to be something stopping the uterus from contracting throughout the whole of pregnancy. So we're focusing on identifying the factors that maintain quiescence. Maybe it's the loss of these factors, rather than some silver bullet, that triggers birth."

The Holy Grail

Magee's Center for Prematurity, which opened in 2002, provides specialized care to women at high risk for preterm delivery, primarily women with a history of giving birth prematurely. In addition to progesterone supplementation, it offers infection screenings, ultrasounds to detect changes in the cervix, and cervical cerclage (a surgical procedure in which the uterus is stitched closed). "Our approach is to prevent prematurity if we can, and even if we can't, to prolong pregnancy and improve outcomes for the baby," Dr. Simhan says.

Preterm birth is expensive. In the United States, the average hospital charge for preterm newborns is $77,000, compared to $1,700 for term newborns.

The approach significantly reduces recurrences. But high-risk clinics can't make a major dent in the national preterm birth rate. That's because most women who deliver prematurely have no reason to suspect that they will. "Most preterm births are first preterm births," Dr. Simhan explains. "We do not have effective screening and prevention strategies for women without a history of preterm delivery. That's the holy grail."

A new multicenter study may help him find that holy grail. Dr. Simhan is among the principal investigators for the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b), established by the National Institute of Child Health and Human Development. Researchers will collect data from 10,000 women who are having their first baby and will look for predictors of preterm birth and other adverse pregnancy outcomes.

Dr. Simhan is particularly interested in how nutritional status influences the mother's immune system and her risk of preterm delivery. He and Dr. Bodnar, an epidemiologist, coauthored a study showing that pregnant women with low levels of vitamin D may be more likely to suffer from bacterial vaginosis, a common infection associated with preterm birth. Vitamin D, which is naturally present in very few foods, is produced by the body in response to sun exposure. "Pittsburgh is one of the grayest cities in America," Dr. Simhan notes. "We have a huge frequency of vitamin D deficiency." The connection between vitamin D and

There are two main types of preterm births. Most preterm births are "spontaneous," occurring as a result of preterm labor or premature rupture of the amniotic sac. About 25 percent of premature births are "indicated," or initiated by health care providers due to problems such as preeclampsia or placental bleeding.

vaginosis may be one reason why African-American women, who need more sunlight than lighter-skinned women to generate the same amount of vitamin D, are more prone to the infection and nearly twice as likely to give birth prematurely.

A deeper understanding of how vitamin D, folate, and other nutrients relate to preterm birth is needed before health care providers can recommend supplementation, he says. "It would be irresponsible to take the data that we have right now and say 'Check your level of this or supplement that.' There is no ready-for-primetime nutritional intervention." For now, his best advice is that women eat a healthy diet, maintain a healthy weight, and begin taking prenatal vitamins before they become pregnant.

He also advises that women heed the signs of preterm labor. "If you're having contractions, bleeding, leak of fluid, or abnormal vaginal discharge, go get examined — even if it's inconvenient, even if it's 2 in the morning — because that's how preterm birth presents for many women. Most women with those symptoms are fine, but you don't know that unless you get checked out."

Ultimately, Dr. Simhan hopes to do more than put NICUs out of business. Preventing preterm birth reduces not only the number of sick babies but also the number of sick kids, teens, and adults. That's because prematurity can have long-term consequences, including learning and behavioral problems, cerebral palsy, vision and hearing loss, and increased risk of obesity, diabetes, high blood pressure, and heart disease. "The benefits of preventing preterm birth are huge," he says. "From a public health perspective, if you can improve the health of a baby, that's 85 years of health outcome." ◆◆

Three groups of women are at greatest risk for preterm delivery: women with a prior preterm delivery, women carrying more than one fetus, and women with certain uterine or cervical abnormalities.

Babies born between 37 and 42 weeks of gestation are considered full term. Those born before 37 weeks are considered preterm, or premature.

In 2009, the most recent year for which data is available, the rate of preterm births in the United States declined for the third straight year to 12.18 percent of all births. After rising by more than one-third from 1981 to 2006, the rate fell 5 percent from 2006 to 2009.