

## HEALTH

# A strong PULSE

A NEW INFERTILITY STUDY AT PENNINGTON ZEROES IN ON PCOS

By ADRIAN HIRSCH

**SINCE THE ONSET** of puberty, Lisa King fought a losing battle of the bulge. By age 22 she "was gaining weight out of control and not able to lose it," she recalls.

"Before my wedding, I put on about 20 pounds. No matter what I did—starvation diet, exercise—nothing got the weight off. After I got married and started having the miscarriages, I would see certain doctors for my weight and [others] for my infertility."

At 82 pounds over her ideal body weight, King was convinced the two issues were connected. After a series of frustrating doctors' visits, she met Charles Aycock, an OB/GYN, who began unraveling the mystery.

Blood work indicated insulin resistance. The diagnosis meant her insulin receptors were not properly converting blood sugar into energy, a condition that was likely to lead to type 2 diabetes. Further testing revealed King suffered from polycystic ovary syndrome. This endocrine disorder is related to insulin resistance and characterized by irregular ovulation and menstrual cycles as well as infertility. Both are biochemical (also called metabolic) dysfunctions common in overweight women.

King was not alone. In fact, this growing trend in infertility is so significant that the National Institutes of Health has awarded the Pennington Biomedical Center more than \$700,000 to conduct a study to understand the role of obesity, body weight and insulin resistance in the regulation of reproduction. Called PULSE, the study is designed to determine how different treatment plans impact women who are infertile due to PCOS.

Like King, "Many women may not know that they have it," explains Leanne Redman, principal investigator of PULSE and head of Pennington Biomedical Research Center's Reproductive Endocrinology & Women's Health Laboratory. "It's a syndrome because it's a cluster of symptoms," she says, "but there's not a single test to diagnose it or a single medicine used to treat it."

Those symptoms can include obesity, irregular menstrual cycles, acne, and male-pattern hair growth along the jawline, back and neck. The diagnosis is best confirmed by an ultrasound that shows limited growth of follicles in the ovaries.

Although clinics as far away as Detroit have sought to enroll their patients in PULSE, the opportunity to participate in this groundbreaking study is exclusively available in Baton Rouge.

The PULSE study derives its name



ERIN PARKER PHOTOGRAPHY

Lisa King and husband Daniel share special moments with daughter Ava. Lisa suffered from infertility due to polycystic ovary syndrome before losing a great amount of weight.

from the fact that the hormones that control reproduction are normally released in predictable pulses. But in women with PCOS, the brain is not releasing hormones at a constant rate. The goal is to restore the natural rhythm.

"We have the chance to find out why people have PCOS by improving it," says Redman. "If we know what improves it, then we can actually help prevent it."

Published in the *Journal of Fertility and Sterility*, Redman's preliminary research demonstrated that when women with PCOS exercised for four months, they lost weight, regained a regular menstrual cycle and improved

their insulin resistance.

In fact, the American College of Obstetricians and Gynecologists reports that even a 5% weight loss can be enough to restore ovulation and fertility.

Diet and exercise, prescription medication and even some types of bariatric surgery have been known to produce similar results. Gastric banding does help patients lose weight; however, the sleeve gastrectomy and gastric bypass often yield greater benefits to the body's biochemistry.

"If you need to lose 30 pounds or less, diets and exercise work every time. It's a matter of sticking to it," explains Baton Rouge bariatric

surgeon Drake Bellanger. "When you start getting above that, that's when the body lays the groundwork to fight you. So, the body's going to sabotage you at every step of the way."

Although surgeons acknowledge the potential for metabolism to thwart weight loss, bariatric procedures were never intended to correct a metabolic imbalance. The surgery was pioneered simply to make the stomach smaller, limit patients' food intake and achieve significant weight loss.

As the procedures became more common, many post-operative patients reported both a reduction in hunger and the resolution of their diabetes.

"[There's something about these

operations] that triggers the sensitivity to insulin," he says. "It's from day one right after surgery that their bodies feel the difference.

"The chemicals that regulate the pancreas [which releases insulin into the bloodstream] are being produced by the stomach," he explains. In overweight individuals, that system is malfunctioning. "After the surgery," Bellanger concludes, "something about the regulation comes back into balance."

With PULSE, Redman is seeking to explain the metabolic trigger for that metamorphosis. It's a question that has intrigued her since the early 1990s, when she pursued her graduate work in Australia under international PCOS authority Robert Norman.

"His clinic was the first ever to do a lifestyle kind of weight loss program for women with PCOS," she recalls. "He observed that these women were starting to get pregnant spontaneously. He discovered [most of the] women were spontaneously ovulating, but that finding wasn't consistent with a change in weight. That's why we're studying now to ask more questions as to why some women are getting their cycles back and some women are not."

Based on her pilot study, Redman hypothesizes a change in insulin or the fat hormone leptin is regulating reproduction.

During 16 weeks of exercising, seven of the eight women resumed their cycles. So researchers started searching for common biomedical indicators among those seven women.

While they didn't lose a large amount of weight, Redman says, "They all significantly increased their insulin sensitivity by 35%. At the same time, they reduced the amount of visceral, male hormone-associated fat they have around the trunk."

She suspects leptin could be the catalyst because research has already shown an injection of leptin allowed women with very low body fat—ballerinas and gymnasts—to regain their cycles without changing their diets. "We know that with obesity, people are leptin resistant," Redman explains. "So I'm going to be looking at the body's fat stores, blood and other metabolic markers, including insulin sensitivity."

The very idea that fat could hold the key to understanding a biochemical reaction represents a relatively new concept in medicine. "When I was in med school, you looked at fat as a dormant issue," says Bellanger. "It was an energy source that was unappealing and unhealthy, but it didn't do anything. Now we know it's an endocrine organ. It can affect the ovaries producing all those sex hormones, and it does the job



Leanne Redman, principal investigator of PULSE, says that one in 14 women of child-bearing age is believed to be affected by PCOS worldwide.

that the ovaries do. When the ovaries have something that does the job for them, they just go on vacation."

Redman hopes to enroll 52 women in the study; however, recruiting patients has proven to be a challenge. Since many women don't even realize they have PCOS, Redman is seeking to identify potential study participants with the aid of dermatologists, who frequently treat women with male-pattern hair growth on their bodies or acne, as well as OB/GYN and internists whose patients' have insulin resistance.

Because the PBRC makes a substantial investment in each participant, researchers must make sure candidates can commit to the rigors and duration of the six-month study. Even if women have the diagnosis, they might not have time or the inclination to keep a food diary, cut calories or come to the center for overnight stays and regular workouts. "We just try to overcome all those barriers with people before we enroll them," explains Redman.

Women who are selected for the

study receive extensive diagnostic and reproductive tests, including MRI, hormonal testing and blood work.

Then, each participant is randomly assigned to one of four different regimens.

One group begins a diet that cuts calories by 25% using the CALERIE program developed at PBRC.

Other women are assigned to work with personal trainers and follow an exercise plan specifically designed to improve insulin resistance.

Two additional groups will receive only medication. Unbeknownst to them, some women will be taking a placebo; others will be given Metformin, a prescription medication used to treat type 2 diabetes. The drug helps control the amount of sugar in the bloodstream, decreases the amount of sugar absorbed from food, and increases the body's response to insulin.

In fact, Metformin was the key to weight loss for Lisa King. Shortly after Aycock prescribed the drug, King began to notice results. "My body started losing the weight. And once that happened, I was able to continue that [process] with diet and exercise. But it took the medicine getting my body more regulated, so I was more successful in losing the weight."

Soon, King's biochemistry changed along with her appearance. After a 30-pound weight loss, all evidence of insulin resistance vanished, so the medication was discontinued. By maintaining her diet and exercise regimen, King lost an additional 20 pounds—for a total loss of 50 pounds in less than a year.

King's reproductive system rebounded as well. At age 25, she gave birth to a healthy daughter.

Pregnancy inadvertently accelerated her weight loss. Nausea during and after the pregnancy resulted in

another 50-pound weight loss, which tipped the scales too far in the other direction. The 27-year-old now weighs 80 pounds less than she did before her wedding.

King won her personal battle against weight gain and infertility before Redman devised her study. Yet King hopes women with PCOS will recognize the value of participating in PULSE.

Besides benefiting from the information revealed from expensive high-tech tests, King says, "The reason people should choose [to enroll] is there's so much [emotional] support that this study will offer you. That is something you don't realize you need until you need it."

King vividly recalls the disdain of family and friends with her inability to fit into her wedding dress, the hopelessness the new bride felt about being unable to control her growing girth, and the devastation of four miscarriages.

"It was a very time-consuming, expensive and emotional process," she says.

"Hopefully this study will figure out a [faster] way to diagnose what each individual person needs," she says. "If there were a better way to just pinpoint exactly what that is, it would save a lot of heartache."



Dr. Drake Bellanger, a bariatric surgeon, says the medical community now recognizes that fat is an endocrine organ that can produce hormones and affect the ovaries.

For more information on study eligibility or to enroll, call the PBRC Clinical Research Call Center at 763-3000 from 8 a.m. to 5 p.m. or visit [pbrc.edu/Clinical\\_Trials/Current\\_Studies.asp](http://pbrc.edu/Clinical_Trials/Current_Studies.asp). If selected, participants will be assigned to either an exercise, diet or medication program for six months and will receive up to \$1,500 for completing the study.