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IN THE LAB

Infertility, Diabetes, Obesity and the Mystery of PCOS

Scientists Look Anew at a Common Problem for Women Trying to Get Pregnant

By SHIRLEY S. WANG



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UCLA professor Daniel Dumesic prepares medication for patient Rachel Dail, left, as part of his polycystic ovary syndrome study. *Reed Hutchinson*

Scientists know this much about polycystic ovary syndrome: It is one of the most common causes of infertility. It's linked to diabetes and several other troubling health problems. It affects as many as 5 million U.S. women.

But the condition, also known as PCOS, largely remains a mystery. Researchers are trying to better understand the disorder, which is generally defined by an excess production of the hormone testosterone, irregular ovulation and cysts—fluid-filled sacs—within the ovaries. Some teams are trying to improve its treatment to lessen its impact on women's reproductive health and metabolism, or how the body uses or makes energy.

"We really need better options," says Esther Eisenberg, project scientist of the Reproductive Medicine Network, a research collaboration set up and funded through the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Even the diagnosis of PCOS can be tricky because the syndrome doesn't look the same in everyone. What is called PCOS is likely a number of different diseases that manifest similar symptoms, such as acne, excess facial- and body-hair growth in reproductive-aged females, insulin resistance and abnormal menstrual periods, according to experts.



Lindsey Maloney was diagnosed with PCOS while in high school. After treatment, she was able to give birth to her daughter Briley, left, now 2. *Brian Maloney*

Facts About PCOS

What researchers know so far about polycystic ovary syndrome:

Of reproductive-age women, 4% to 10% or more are estimated to have PCOS.

PCOS is likely caused by a number of diseases that manifest in similar physical symptoms.

The syndrome is defined by high levels of androgen production, irregular ovulation and cysts in the ovaries.

Symptoms of PCOS may include infertility, insulin resistance, weight gain/obesity, acne and excess hair growth.

Diagnosis may involve blood tests to measure androgen and glucose levels and imaging of the ovaries.

Current treatment options include diet and exercise, birth control pills, the diabetes drug metformin and anti-androgen medicines.

Over 60% of women with PCOS are overweight or obese. Excess hair growth, called hirsutism, also can differ by ethnicity, as can body weight. Such demographic differences can cause doctors to have difficulty identifying PCOS in those patients. And since most girls have irregular periods when they first start menstruating, misdiagnosis may be more likely to occur with young adolescents.

Insulin resistance, an inability to properly process sugar, is common, regardless of body weight. This can greatly raise the risk in PCOS patients of developing diabetes. The uterine lining may build up excessively, which is related to the lack of ovulation, and endometrial cancer risk appears to be increased as well. And women with PCOS often have trouble conceiving because they may not ovulate regularly, and may be more likely to miscarry. There also are concerns about an increased risk of heart disease, although no definitive data support that notion.

Researchers fear a general rise in obesity is causing a spike in PCOS, too, though they don't have enough longitudinal data to say definitively.

PCOS appears to have a genetic component that may be triggered or influenced by environmental factors, like weight gain, later in life. But scientists are still trying to determine exactly what goes wrong. The symptoms of PCOS are at least in part due to excess androgens, the family of hormones to which testosterone belongs.

The womb environment also appears critical to its development. Daniel Dumesic, a professor of reproductive endocrinology and infertility at the University of California, Los Angeles, and his colleagues found that by exposing mother monkeys with high doses of testosterone, their female offspring developed PCOS-like features after birth, including higher testosterone levels.

Audio

Shirley Wang tells WSJ This Morning's Gordon Deal about the complications associated with PCOS.

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They now are studying whether the bodies of women with PCOS, because of excess testosterone, store fat in tissues where it shouldn't be. Dr. Dumesic hypothesizes that this may impact the function of the ovary and perhaps fertility.

Christopher McCartney, a professor of medicine at the University of Virginia, is examining whether the high levels of testosterone could increase the body's secretion of another chemical, called luteinizing hormone, or LH, at puberty, contributing to the development of PCOS. LH, in turn, is needed for the ovaries to produce testosterone, so high levels of LH may be helping produce additional testosterone, leading to a vicious cycle, Dr. McCartney says.

Why the syndrome increases the risk of diabetes remains unclear. One possibility is that because the body doesn't respond well to insulin, it overcompensates to make more of it, which leads to increased levels of luteinizing hormone and lower levels of follicle-stimulating hormone, as well as increased ovarian production of androgens.

Together, these slow or prevent ovulation, according to Richard Legro, a professor of obstetrics and gynecology and public health sciences at Penn State University College of Medicine in Hershey, Pa.

"It's likely that the menstrual and reproductive dysfunction is a harbinger of later metabolic abnormalities like diabetes," Dr. Legro says.

Treatments include hormonal contraceptives to prompt ovaries to stop producing testosterone and other hormones, plus anti-androgen medications like flutamide, usually used to treat prostate cancer, and insulin sensitizers for metabolic issues. Metformin, which isn't an insulin sensitizer but is used to treat high blood sugar, is given as well on a case-by-case basis. Some of these treatments carry risks and most, with the exception of metformin, can't be used when women are trying to get pregnant.

Lourdes Ibáñez, a professor of pediatrics at the University of Barcelona, has been studying combination treatments for PCOS. She found that metformin, an insulin sensitizer called pioglitazone and flutamide taken together performed better than oral contraceptives. Oral contraceptives appeared to actually worsen the girls' metabolic abnormalities.

Six months after the 18-month treatment, no one in the combination therapy group has relapsed but 50% of those in the oral contraceptive groups have, according to a paper Dr. Ibáñez published in 2013 in the *Journal of Clinical Endocrinology & Metabolism*.

She is also studying whether the symptoms of PCOS can be prevented in girls at high risk for the condition. She conducted a tiny pilot study of 38 girls who were born with a low birth weight and had precocious puberty, which are often precursors to PCOS.

She began treating them with metformin between ages 8 to 12. At 18 years old, the rate of detectable symptoms in the treated group was 5%, compared with 50% of those in the untreated group. She hopes to run a larger trial to further explore the possibility of prevention.

Scientists also have focused on improving fertility in women with PCOS. With clomiphene citrate, the most commonly used agent for ovulation induction in women with PCOS, only about half the women who ovulate end up having babies, according to NICHD's Dr. Eisenberg.

Dr. Eisenberg, Penn State's Dr. Legro and the Reproductive Medicine Network have been running a clinical trial to improve fertility. In a presentation to the American Society for Reproductive Medicine in October, they showed that early results indicate a medication called letrozole, a drug commonly used for in vitro fertilization, appears to result in more live births than clomiphene.

One of those success stories was Lindsey Maloney, from Fredericksburg, Va. She had so much facial hair she started waxing it off in the fifth grade and always struggled with her weight because of insulin resistance. She had her period only once in the seventh grade and was first diagnosed with PCOS at 15.

When Ms. Maloney, now a 29-year-old school counselor, got engaged to her now-husband, her fertility worried her. When the couple heard about Dr. Legro's study, Ms. Maloney enrolled and drove three hours to Hershey once a month for drugs to help her ovulate. She was randomly assigned to the letrozole group, she says.

They now have a 2-year-old girl, Briley. Ms. Maloney and her husband are trying for a second child on their own and haven't had any luck yet.

Ms. Maloney has been taking metformin since she was a teenager, sees an endocrinologist every three months and buys supplements and organic foods without hormones in them, but her symptoms have remained, she says.

"It's not just on your ovaries. It's a whole mess of endocrine problems that you have," she says.

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