



Dr. Pisarska investigates premature ovarian failure and premature ovarian aging as it relates to infertility.

which offers complete diagnostic, treatment, and management services for a full range of reproductive health concerns. Their patients with infertility mirror the national picture: About one third are women who have problems with ovulation, about one third are males with fertility issues, and about a third are women with tubal disorders and uterine endometriosis.

FERTILE GROUND

Dr. Pisarska's research specialties include premature ovarian failure and premature ovarian aging as it relates to infertility. In premature ovarian failure, the ovaries stop functioning in women under 40, while in premature ovarian aging, the ovaries and ova (the eggs) are not as young and healthy as would be expected for the woman's age.

To understand these conditions, Dr. Pisarska studies folliculogenesis—how the unfertilized ovum develops from its earliest stages in the ovary. She also investigates why some ova develop prematurely and then die. Pisarska notes that women actually begin losing ova before birth. A female fetus has seven million to eight million ova, a newborn has one million to two million, and a teenager has 300,000. Over a woman's reproductive lifespan, in every month that she releases an ovum for potential fertilization, 1,000 others deteriorate. In her late 30s, the loss starts to accelerate. Scientists cannot yet explain why this occurs.

"A gene termed Forkhead L2 is associated with the early loss of eggs," says Pisarska. "I have found that there are factors that regulate this gene and help keep the egg quiescent and restrain it from continuing development and degeneration. I am looking at how these factors work to turn this gene on or off. If we can understand how these different factors work together, then we might be able to manipulate them to prevent premature egg degeneration."

THE FRAGILE EMBRYO

The fragility of the embryo is clear: Many women who begin the IVF process do not successfully complete it because the fertilized egg fails to implant in the uterus. In 2003, out of more than 74,000 women who underwent embryo placement during IVF, implantations resulted for only 31,000. Such figures sparked Dr. Kao's research into understanding how the embryo recognizes the lining of the uterus.

Scientists have long known that women have a "window of implantation"—days 20 to 24 of their menstrual cycle—when an embryo will implant in the uterus. Kao's first related research observation was that hundreds of genes expressed in the lining of the uterus were involved in this window. The lining of the uterus and the surface of the embryo together create a system similar to Velcro, enabling the embryo and lining to adhere.

"It turns out that one of the 12 genes gets expressed as an enzyme and supports this Velcro process," says Kao. "So my major research focus is: What regulates this particular gene? What makes it get turned on or off, or partially turned on or off? If we can figure this out, then maybe we can get the lining of the uterus to make more of the enzyme and make the 'Velcro system' stronger. Then, when an embryo comes along, it will adhere and grow into a healthy fetus."

With the three Cedars-Sinai investigators each examining different aspects of fertility, "our studies complement each other and give a broader and more in-depth understanding of problems affecting women's reproduction," Dr. Azziz says. "The work is 'translational' because we're examining patients and solving their real clinical problems in the laboratory. We don't know how soon these molecular studies will point to new therapies, but clearly this research is where we must begin." ✎



Polycystic Ovary Syndrome has now been recognized as perhaps the most common of all hormonal disorders affecting women. Cedars-Sinai is at the forefront of research into future cures for this little-known yet significant disorder.

BY IDELLE DAVIDSON

Bearded ladies are the stuff of history and legend. For generations they fascinated audiences at carnivals and sideshows. But excess hair that is dark and thick on the face and on other parts of the body—a condition called hirsutism—is in fact a serious disorder. Chances are that these women had Polycystic Ovary Syndrome (PCOS), a potentially serious hormonal disorder occurring during the reproductive years. Specifically, PCOS is an excess-androgen disorder. Androgens are male hormones. Low levels are normally encountered in a woman's bloodstream. Excessive amounts, however, can have severe health consequences.



"We are trying to understand what makes this disorder what it is. If we know the causes and consequences, we can design better therapies."

— Ricardo Azziz, M.D., M.P.H., M.B.A.



"We now know that PCOS is a complex disease, meaning that several genes are involved, not just a simple mutation in one gene. Finding those genes is the challenge. We're looking for a bunch of needles in a very large haystack."

— Mark Goodarzi, M.D., Ph.D.

PCOS is the most common hormonal disorder of females of childbearing age, affecting about seven percent of this population. It is the number one cause of excess hair growth and the single most common cause of infertility in women. Reaching menopause does not help. Symptoms lessen, but the associated risk of diabetes and heart disease increases dramatically.

Yet, few women seek proper medical attention for this condition. Instead, they rely on cosmetic solutions for hair removal or ovulation drugs from their doctors for infertility. They treat the symptoms but not the cause.

Ricardo Azziz, M.D., M.P.H., M.B.A., has been investigating PCOS for 20 years. He is chair of the Department of Obstetrics and Gynecology at Cedars-Sinai and holder of the Helping Hand of Los Angeles Chair in Obstetrics and Gynecology. He is also director of the Division of Reproductive Endocrinology.

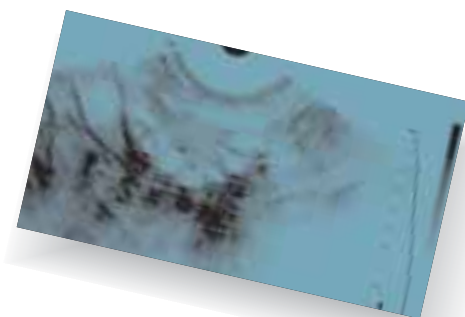
Two years ago, Dr. Azziz founded the Center for Androgen-Related Disorders. Under Azziz's direction, the center has grown into the only one of its kind on the West Coast, offering in-depth testing, comprehensive treatments and support, and research into molecular mechanisms and future therapies. Only a handful of similar programs exist in the country.

"It is vital that we get the word out about PCOS," says Azziz. "So many women have no idea that this is a hormonal disorder with lifelong and serious implications."

These implications are also wide ranging. Young women with PCOS often show a decreased sensitivity to insulin, the hormone that regulates blood sugar. Their muscle, fat, and liver cells do not use insulin

properly; the pancreas tries to keep up with the demand by producing more insulin. Eventually, excess glucose builds up in the bloodstream, resulting in high levels of blood glucose and high levels of insulin circulating in the blood at the same time. High insulin levels adversely affect the ovaries, the skin, and the blood vessels. Left untreated, this can lead to adult-onset diabetes, high blood pressure, and heart disease. The incidence of diabetes is five to seven times higher in women with PCOS.

Tests can also reveal high levels of bad cholesterol and low levels of good cholesterol in women with PCOS. This, together with the high levels of insulin, ups the risk of a heart attack or stroke. Women with PCOS who do not ovulate or who miss their cycles are also at higher risk for developing uterine cancer.



The name "Polycystic Ovary Syndrome" is derived from the appearance of the ovaries in many women with the disorder—large and studded with numerous small cysts (polycystic). These cysts are fluid-filled sacs that contain immature eggs.

FINDING NEEDLES IN A HAYSTACK

There is as yet no cure for PCOS. But thanks to clinical and basic research, scientists at Cedars-Sinai are discovering ways to manage symptoms and prevent complications.

Fifteen years ago, Dr. Azziz initiated one of the largest PCOS studies reported, with more than 1,000 patients evaluated. With DNA derived from 600 subjects, he and his colleagues hope to identify genetic differences among these women.

"We are trying to understand what makes this disorder what it is," says Azziz. "If we know the causes and consequences, we can design better therapies."

Denis A. Magoffin, Ph.D., director of the Reproductive Endocrinology Research Laboratory at Cedars-Sinai, is known internationally for his research on PCOS. Working in the laboratory with the cells that produce androgen in the ovaries, he traces the way by which insulin and other factors regulate androgen production. "Women produce androgens in two organs: the ovary and the adrenal gland," says Magoffin. "In PCOS, there is little doubt that the excess androgen comes primarily from the ovary. Once we understand why ovarian cells are making too much androgen, we can try to go in and reverse it," he says.

Although PCOS is primarily a genetic disorder, environment also plays a role. In a study reported in the journal *Fertility and Sterility*, Dr. Azziz and his colleagues found that in 93 patients with PCOS, 78 of their mothers and 50 of their sisters also had the syndrome. Other studies report that daughters have a 50 percent chance of developing PCOS. "So half never get it," says Azziz. "It's important to emphasize the positive."

Mark O. Goodarzi, M.D., Ph.D., a physician in Cedars-Sinai's Division of Endocrinology, Diabetes and Metabolism, works with Dr. Azziz to investigate the genetic component of PCOS. "We now know that PCOS is a

"In PCOS, there is little doubt that the excess androgen comes primarily from the ovary. Once we understand why ovarian cells are making too much androgen, we can try to go in and reverse it."

— Denis Magoffin, Ph.D.

complex disease, meaning that several genes are involved, not just a simple mutation in one gene," he says. "Finding those genes is the challenge. We're looking for a bunch of needles in a very large haystack."

Population studies help narrow the search. Goodarzi, Azziz, and Jerome I. Rotter, M.D., who is director of research at the Cedars-Sinai Medical Genetics Institute, along with colleagues at UCLA, administered a questionnaire to 156 young Mexican-American women. About 13 percent reported symptoms of PCOS. That's nearly double the prevalence of PCOS in African-Americans and non-Hispanic whites, possibly related to the fact that Mexican-Americans have high rates of insulin resistance and type 2 diabetes. "We found that Mexican-American women were at an increased risk for PCOS," says Azziz. "Our study was the first to look at this population and make that connection."

And in the last 20 years, Dr. Azziz and others fascinated by this complex disorder have checked off a few other milestones. They identified the relationship between PCOS and insulin resistance; they understood that it was due to a variant within adipose (fat) cells; and they documented the numbers of women affected.

At age 19, the Uruguay-born clinician and scientist was then the youngest student to ever attend medical school at Pennsylvania State University. "I had great role models," says Azziz. His father is a nuclear physicist and his mother is an anthropologist. "They taught me the value of using my head, my hands, and my heart," he says.

"I chose this field because I found it rich and promising—an undiscovered country with significant medical impact," adds Azziz. "When you are passionate about something, you are always driven to pursue it." 