



Lee-Chuan Kao, M.D., and Margareta Pisarska, M.D. (foreground), confer with (L to R) postdoctoral researcher Winifred Mak, M.D., Salma Khan, Ph.D., and student affiliate Parham Zarrini.

Charting the New Frontiers of Fertility

For more than two decades, medicine has been offering hope and help to infertile couples through drug treatment, surgery, and the widely publicized procedure of in vitro fertilization (IVF). While IVF has brought the joys of parenthood to many, the procedure results in a healthy pregnancy in just 35 to 40 percent of women under 35, and significantly less often for older women. Recognizing that much more needs to be known about the causes of infertility and pregnancy loss, Cedars-Sinai physicians are on the hunt for answers.

BY ROBIN HEFFLER

To produce a pregnancy through IVF, each step of the process must be successful: receiving hormone injections that stimulate egg production, successfully harvesting them for fertilization with sperm in the laboratory, and then transferring the resultant embryos into the woman's uterus to grow into a full-term baby.

Since the first babies were conceived through IVF 26 years ago, scientists have made significant advances and are focusing on quality over quantity. They have developed more purified forms of hormonal stimulants. Embryos are being grown longer in the laboratory to increase their viability when they are placed in the uterus and to avoid the risks

of pregnancies with multiple fetuses. There are also procedures to screen embryos for genetic diseases.

"There is a new frontier in reproductive medicine," says Ricardo Azziz, M.D., chairman of the Department of Obstetrics and Gynecology at Cedars-Sinai. He studies hormonal abnormalities that interfere with fertility, as well as one of the most common causes of infertility, Polycystic Ovary Syndrome (see story on page 19). "We are beginning to discover the molecular mechanisms that underlie this pervasive and common disorder."

Two of Azziz's colleagues, Dr. Margareta Pisarska and Dr. Lee Kao, are co-directors of the Cedars-Sinai Center for Fertility and Reproductive Medicine,



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.