ivf innovations

These seven advances –some already here, a few still to come–are aimed at changing the practice of in vitro fertilization. Their goal: to help even more couples become parents.

By Lorie A. Parch

Being a fertility patient these days almost requires a science degree. How else could anyone keep up with the latest technology and scientific advances affecting assisted reproductive technology (ART)? Perhaps no area is changing faster than in vitro fertilization (IVF). There are fancy new incubators for labs; increasingly better, more refined tests; even so-called "minimal stimulation IVF," which uses far fewer drugs and works in sync with a woman's own cycle. As diverse as the seven innovations profiled below may be, they all have one goal in common: to bump up the pregnancy rate, which still stubbornly hovers around 30 percent for a round of standard IVF. A number of the techniques aim to raise the bar even higher: upping the IVF pregnancy rate while lowering the numbers of multiple births. If you don't recognize any of these innovations at your own fertility center, just wait. Chances are, one or more of them will be coming your way soon.

embryo markers and single embryo transfer (SET)

What They Are: Single embryo transfer (SET) aims to identify the embryo most likely to implant and result in a healthy pregnancy before the embryo transfer stage of IVF; then, a single embryo is transferred back to the uterus. Embryo markers are ways to identify which embryos are most likely to implant and grow into a viable pregnancy.

Details: One embryo marker has been identified by Geoffrey Sher, M.D., executive medical director of the nationwide Sher Institutes for Reproductive Medicine. Dr. Sher's research has focused on how the amount of HLA-G (human leukocyte antigen-G) made by an embryo indicates the likelihood that the embryo will implant and grow into a healthy baby. "When HLA-G gets into the system, it makes a pitch to [a woman's] immune system and [that might be] the pitch the embryo makes for acceptance," he says. Dr. Sher and his colleagues are also working to refine a process of comparative genomic hybridization (CGH), which would allow an embryologist to quickly look at all of an embryo's chromosomes (something preimplantation genetic diagnosis—see page 92—currently can't do) and identify the embryos most likely to do well.

Another embryo marker system actually examines cells in the culture media that the embryos have grown in, rather than the embryos themselves. Molecular Biometrics, has developed a special type of spectrascope that analyzes molecular patterns that studies have correlated with successful pregnancies. The company hopes to have its spectrascope in reproductive endocrinologists' offices soon.

Why It's Better: One top goal among fertility experts is reducing the number of embryos that are implanted in IVF, thereby dropping the chance of high-risk multiple births (twins, triplets, and higher) without reducing the pregnancy rate. Embryo markers and SET can help achieve that. Says Mike R. Soules, M.D., managing partner of Seattle Reproductive Medicine and a past president of ASRM, "There's a total consensus that a singleton birth is best if you can get it. If you look at the major complication of pregnancy, it's multiple pregnancies and that relates back to how many embryos you transfer. If a lab has a good pregnancy rate at the expense of a high multiple rate, that's not a good program."

coculture

What It Is: Before starting a round of IVF, a sample of a woman's uterine (endometrial) lining is removed and then frozen. "The patient then undergoes a typical IVF cycle; her eggs are retrieved, mixed with sperm, and our lab begins to thaw and grow the endometrial cells," explains Larry I. Barmat, M.D., director of coculture and the donor egg program at Abington Reproductive Medicine near Philadelphia. After fertilization, the embryos are placed on top of the patient's own uterine cells to grow. "Coculture is a way to provide a different environment for your embryo(s) to grow in; it's a little closer to the natural environment," says Dr. Barmat.

Details: In a study Dr. Barmat conducted of women 38 and younger, the pregnancy rate was comparable to his other IVF patients—a little over 60 percent, he says. If you're 38 years old or younger and interested in participating in a year-long study comparing coculture to standard IVF, contact Dr. Barmat at Abington Reproductive Medicine (www.abington-repromed.com). Patients not enrolled in a study can expect to pay $2000 for coculture at Abington.

Why It's Better: So far research only points to some success with patients who have previous failed IVF cycles and/or those with poor-quality embryos. But for these couples, coculture offers a measure of hope. Says Dr. Barmat, "With coculture the embryos seem to grow quicker and be less fragmented. The answer of whether pregnancy rates are improved, though, is still a debate."

intravaginal culture / INVOcell™ / conception capsule

What It Is: "Egg(s) and sperm are placed in a device called INVOcell, a sort of thumb-sized plastic capsule that's inserted into the vagina," explains Peter Ahlering, M.D., medical director of Sher Institutes for Reproductive Medicine in St. Louis and central Illinois. "The vagina is the right temperature, has the right percentage of carbon dioxide, and is not subject to some of the problems we have with incubators [for facilitating fertilization]," adds Randy S. Morris, M.D., medical director of IVF 1 in Chicago and Naperville, Illinois. A woman using INVOcell is outfitted with a perforated diaphragm-like device to keep the capsule in place. When the capsule is removed from the vagina three days later, fertilization should have taken place.

Details: Although intravaginal culture has been studied in a number of fertility centers, it's not yet approved by the Food & Drug Administration (FDA) and is still available only through trials. Dr. Morris calls the data so far too limited to advise a patient to use IVC over a traditional IVF protocol.

Why It's Better: INVOcell may appeal to certain religious groups, since fertilization happens in a woman's body, not in the lab. There's also a potential cost sav-

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ivf 101

A standard round of in vitro fertilization (IVF) starts with suppression of a woman's normal menstrual cycle using birth control pills and other drugs to stop the production of the hormones FSH (follicle stimulating hormone) and LH (luteinizing hormone). This allows the doctor to control the timing of the IVF cycle. Next comes medication to stimulate the growth of the follicles, which contain the eggs. During this time frequent monitoring—blood tests and vaginal ultrasounds—track the number and size of the follicles. When the follicles reach the right size, ovulation is induced with hCG (human chorionic gonadotropin). About 34 to 36 hours later, the egg retrieval takes place. The eggs are then taken to the lab to be fertilized with sperm, and the fertilized eggs are left to grow in the lab, usually for two to five days. Normal embryos are then transferred back to the woman's uterus. About two weeks later a blood test will determine whether or not pregnancy has occurred.

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ings since less lab work is needed. And intravaginal culture may make IVF available to couples who don't have easy access to high-tech labs.

in vitro maturation (IVM)

What It Is: A woman's eggs are retrieved when her follicles are significantly smaller than in a standard round of IVF. "Instead of fertilizing them right away, there's an additional day in the lab where they mature in a special [solution]," explains Jessica Macdonald, B.S., T.S.(ABB), supervisor of reproductive laboratories at Delaware Valley Institute of Fertility & Genetics in Marlton, New Jersey. The eggs are then fertilized using ICSI [intracytoplasmic sperm injection] and the embryos transferred back to the uterus.

Details: With IVM you'll follow your natural menstrual cycle; you'll also get less stimulation medication to help the follicles grow, and no medication to kick off ovulation, says Macdonald. A number of fertility centers offer IVM nationwide; since it's considered a variation of IVF, it doesn't require FDA approval.

Why It's Better: For women with polycystic ovarian syndrome (PCOS) and others at increased risk of ovarian hyperstimulation syndrome from the high amounts of follicle-stimulating medication typically used in IVF, IVM is a better choice, asserts George S. Taliadouros, M.D., medical director of the institute. "A PCOS patient that goes through IVF has a lot of follicles, but most of the eggs in them are not good," he explains. "With IVM you won't get as many eggs, but the eggs are better quality." Less medication means real cost savings for IVM patients, who pay under $1000 at the institute, versus about $5000 for a full course of IVF drugs. "We're also seeing them half as many times [for monitoring]," says Dr. Taliadouros, so patients save time and, potentially, money if they pay for each ultrasound and blood test.

preimplantation genetic diagnosis (PGD)

What It Is: A method to determine whether your embryo(s) has chromosomal abnormalities, such as Down syndrome, or a single-gene disorder, such as cystic fibrosis. PGD can also be used to select the sex of an embryo. In the lab, an embryologist removes one or two cells from a day-3 or day-5 embryo and usually sends it off to a lab for analysis, explains Susan A. Gitlin, Ph.D., a research scientist at the Jones Institute for Reproductive Medicine at Eastern Virginia Medical School in Norfolk.

Details: The Genetics & Public Policy Center at Johns Hopkins University estimates that 4 to 6 percent of all IVF cycles now include PGD. This high-tech analysis comes at a price, though: about $4000 to $5000 above usual IVF fees. Keep in mind that PGD can't put to rest all fears of heritable problems: "There are a certain number of tests we can do right now, ranging from 9 to 13 chromosome pairs," Gitlin says–a relatively small percentage of an embryo's total of 23 pairs. "We can't say that there aren't problems in the chromosomes we can't test for, but the odds of the non-tested chromosomes having an error are lower than the tested ones." Mutations on the chromosomes that can be tested with PGD account for about 85 percent of all abnormalities seen in fetuses or babies. The risk of damage to the

embryo is small, Gitlin adds, with over 98 percent surviving the process.

Why It's Better: Many patients first talk about PGD with a genetic counselor, says Gitlin, especially if they have a family history of cystic fibrosis, Tay-Sachs, hemophilia, sickle cell anemia, or another genetic disorder, or if the woman is older. Multiple rounds of failed IVF may be another reason to investigate embryo quality with PGD, too.

Org 36286

What It Is: A once-a-week injectable follicle-stimulating medication.

Details: "Org 36286 has a longer half-life [than other follicle-stimulating medications], and due to this it's able to cover the first week of treatment. It would mean just one injection for one week instead of daily injections," says Eric H. Hoomans, M.D., director, medical affairs for global venture team fertility at the Dutch company Organon, which makes the once-weekly drug. Though early research has been completed, the company is just beginning the FDA approval process for Org 36286, says Dr. Hoomans; the drug isn't expected to be available on the U.S. market until 2008, and it's still not known how much it will cost, what dosage is ideal, and who it's best for. Three locations of the Southern California-based Huntington Reproductive Center Medical Group are currently leading a clinical trial of Org 36286 in qualified IVF patients.

Why It's Better: The drug, which comes in a "pen" device like that used for Follistim, "gives patients far more freedom, and less obsession with injections, less anxiety about needles and concerns about correct dosing," asserts Dr. Hoomans.

subendometrial embryo delivery (SEED)

What It Is: During an embryo transfer, a very thin endoscope is inserted through the cervix into the uterus, allowing the doctor to find an ideal spot in the uterine lining to deposit the embryos, usually somewhere near the top of the uterus "where it's soft and spongy," says Michael M. Kamrava, M.D., medical director of West Coast Infertility Medical Clinic in Beverly Hills, California, and the creator of SEED. Then a second needle catheter containing the embryos is added to the endoscope's catheter and the embryos are painlessly inserted into the uterine lining.

Details: To date, Dr. Kamrava has studied SEED in about 350 of his patients. If two or three good-quality embryos are implanted, he says, "there's an almost 80 percent chance of pregnancy, about 30 percent higher than regular IVF." Several universities may be studying and using SEED in 2007, Dr. Kamrava says; for now, the only place to receive it (at no extra cost to IVF) is at his Beverly Hills clinic.

Why It's Better: With his improved endoscope, "I can see where I'm going and maneuver whatever way the uterus curves," Dr. Kamrava says. "The uterus is not a flat surface. If the embryos are just released on the surface, some are lost, some go into the fallopian tubes, some implant in the lower part of the uterus and cause placenta previa." With SEED, he adds, "the embryo is inside the lining of the uterus and it's not going to move," alleviating the need, too, for bedrest after a transfer. Since there's more certainty about embryos not being lost, Dr. Kamrava says fewer need to be transferred, reducing the chances for multiple births. C