Delaware Valley Institute of Fertility & Genetics
Conceptions
Summer 2004

A Breakthrough in IVF

What you need to know about blastocyst culture and transfer.

By Sangita K. Jindal, Ph.D., director of DVIF&G's Reproductive Laboratories

In natural conception an egg is released from the ovary and is picked up by the fallopian tube where it is fertilized by sperm swimming down to meet it. The fertilized egg, or embryo, begins to develop in the tube as it gently floats for six to eight days to the uterus. There it implants into the uterine wall, and pregnancy occurs.

In *in vitro* fertilization (IVF) once a single sperm in the lab fertilizes an egg normally, it begins to divide sequentially from one cell on the first day to a five to eight cell embryo by the third day of culture. Embryos conceived through IVF are routinely transferred into the uterus on day three, when they usually achieve the eight-cell stage of development. Implantation rates in these patients are typically 20 percent. It's possible that premature exposure of these cell-stage embryos to the uterus on day three compromises embryo development and viability.

A major breakthrough occurred in human IVF with the development and use of sequential media for embryo culture. This scientific advance allows embryos to be cultured in the lab up to day six until they reach the blastocyst stage of development. These media take into account the physiological changes that occur in energy requirements and metabolic capacity of the embryo as it develops from the early fertilized egg to blastocyst, as well as the changing environment within the female tract as the embryo passes through.

The Making of a Blastocyst

It has been determined that amino acids (the basic component of proteins) and carbohydrates (sugars) are among key regulators of embryo development in humans. Currently, media is designed to be used sequentially. The first media is used to culture the egg and embryo until day three of development to the eight-cell stage. The second media is used to develop this cleavage-stage embryo to the blastocyst stage of development.

Following the cleavage-stage of development an embryo forms a morula followed by a blastocyst. A morula has cell-cell membranes that are indistinguishable from each other, and the entire embryo is a tightly formed ball of cells (a phenomenon known as compaction). Approximately 24 hours after the morula has formed and compaction has taken place, the intercellular spaces begin to enlarge to create a central fluid-filled cavity called the blastocoel. The cells of the developing blastocyst form a shell enclosing the blastocoel, one pole of which is distinguished by a thicker accumulation of cells which becomes the inner cell mass. The outer ring of cells comprises the trophoblast. The inner cell mass will become the fetus, and the trophoblast will become the placenta.

Visible cells, a small irregular fluid-filled blastocoel, and a thick zona pellucida or glycoprotein matrix that surrounds the egg and the developing embryo characterize early stage blastocysts. Due to the accumulation of fluid in the now large blastocoel, later-stage blastocysts are

considerably larger than cleavage-stage embryos or early blastocysts. The cells lining the cavity are too numerous and thin to count, and the zona pellucida surrounding the blastocyst has thinned in response to the pressure exerted by the increased volume of fluid.

The Benefits of Blastocyst Culture and Transfer

The advantages of blastocyst culture and transfer on day five include the synchronization of the embryo with the female tract leading to increased implantation rates; decreased uterine contractility on day five; less cervical mucus during day five transfer; and only the strongest, healthiest embryos have the ability to grow into a blastocyst after five days of culturing under optimum conditions. This "natural selection" of embryos boosts the success rates of transfers and eventual healthy deliveries.

Blastocyst culture is an integral part of pre-implantation genetic diagnosis (PGD). Embryos are biopsied for PGD on day three, and the results of the analysis are typically reported late on day four or early on day five. With this information at their disposal, these patients receive a blastocyst transfer of healthy embryos with no known genetic abnormalities. Blastocyst culture allows for improved assessment of embryo viability prior to transfer. At the four to eight-cell stage, the embryo is starting to activate its own genome as opposed to being under the control of the inherited genome of the egg. After the eight-cell stage, the embryologist is assessing true embryo physiology. Blastocyst culture supports embryonic self-selection, resulting in hardier embryos that can be transferred to the uterus in fewer numbers.

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Between 1980 and 1997, the number of twin births in the United States increased 52 percent, and the number of triplet and higher-order multiple births increased 404 percent, mostly among women age 30 and above. The use of assisted reproductive technologies is clearly associated with the increase in multiple births. Multiple gestations are linked to increased rates of fetal death; gestational diabetes; pre-eclampsia; preterm delivery; cerebral palsy; increased stress; psychological distress; and health costs.

Blastocyst transfer helps to reduce the number of higher-order multiple pregnancies. It is possible that the transfer of a single high-quality blastocyst can achieve good pregnancy rates. This option may be a good choice for young women for whom multiple gestations would pose serious health risks.

Blastocyst Transfer Is Not For Everyone

The higher rates of implantation and pregnancy associated with the transfer of blastocysts compared with earlier cleavage-stage embryos have led many fertility centers to adopt this procedure for some or all of their IVF patients. While blastocyst culture and transfer is beneficial for some patients, it may not be appropriate for all patients because the extended culture may compromise the implantation potential of the embryos. For some patients, the uterus may be a better embryo incubator than the environment created in the lab. These patients may produce less eggs due to age or to other factors and therefore risk having no embryos to transfer at the end of their IVF cycle. The best candidates for day five blastocyst transfers are those with several high quality, advanced (6 to 8 cell) embryos on the third day of culturing. These patients are usually in their early 30s or younger.

Given our current technologies there is a role for both day three and day five embryo transfers in IVF. Each may be appropriate for a specific patient population.

Sangita K. Jindal, Ph.D. recently joined DVIF&G as Director of its Endocrine, Andrology, and Embryology labs. Accredited by the American Association of Bioanalysts as a High Complexity Lab Director (HCLD), Dr. Jindal is responsible for meeting DVIF&G's high standards of quality and success in its state-of-the-art lab facilities.

In addition to her clinical responsibilities, Dr. Jindal is dedicated to improving care for fertility patients and is currently conducting research into the phenomenon of ovarian aging. She has been awarded several grants in this area and has published her work in peer-reviewed scientific journals.

Dr. Jindal received her Ph.D in reproductive physiology at the University of Toronto's Banting and Best Institute of Medical Research, where her focus was on the role of growth factors in ovarian cancer.

She has worked as Laboratory Director and Senior Embryologist for IVF programs at UMDNJ-Newark, Hackensack University Medical Center and Montefiore Medical Center. Dr. Jindal is a Clinical Assistant Professor in the Department of OB/GYN & Women's Health at the Albert Einstein College of Medicine in New York City.

In her role as director of DVIF&G's Reproductive Laboratories, Dr. Jindal performs blastocyst culture and transfer. If you have any questions regarding the blastocyst procedure, please contact Dr. Jindal at (856) 988-0072.

Gene Found That Regulates Aging and Fertility

Researchers from the Mayo Clinic in Rochester, Minnesota have discovered a gene that they believe is responsible for the onset of aging, including age-related disorders such as infertility, reproductive problems, and cataracts. Their findings are found in the July issue of the journal *Nature Genetics*.

Funded by a grant from the National Institutes of Health (NIH), the research was conducted in genetically modified mice. The results show promise in helping physicians understand and treat infertility and other aging-related conditions in humans.

The researchers discovered that the BubR1 gene controls the production of a protein that modulates physical aging. The mice studied lacked normal levels of that protein and began to age prematurely. They also found that levels of the gene decreased as normal mice age naturally. Based on these findings, the Mayo team believes that this protein may bring on some of the physiological effects of aging.

The scientists also found that mice with low levels of BubR1 protein are infertile and cannot distribute chromosomes properly when their germ cells divide. Abnormal numbers of chromosomes in germ cells are a hallmark of reproductive aging in humans, and the primary cause of increased still births and birth defects, such as Down syndrome, in women over age 35.

The researchers plan to conduct further studies involving the BubR1 gene and its effect on aging-related conditions, including infertility. With a further understanding of the link between the gene and age-related reproductive problems, they hope to develop treatments to help infertile couples conceive.

Another Reason Not to Smoke

Pregnant women who smoke may be jeopardizing their baby's future fertility, according to a new study of males in five European countries. The researchers found that adult sons of women who smoked while pregnant were more likely to have smaller testes and reduced semen quality than other men.

Smoking while pregnant also is linked to greater risk of preterm delivery and low birth weight. Women who are trying to conceive also should stop smoking. Smoking has been linked to female infertility.

Corley Joins DVIF&G

DVIF&G recently welcomed David R. Corley, M.D., FACOG as director of its Early Pregnancy Loss and Gestational Wellness program.

An expert in early pregnancy loss and gestational wellness, Dr. Corley is a reproductive endocrinologist with extensive experience in vitro fertilization (IVF) and in working with infertile couples.

A graduate of the University of South Carolina School of Medicine, he received his postgraduate training in Obstetrics and Gynecology at the Naval Medical Center Portsmouth Charette Health Care Center and at the University of Louisville School of Medicine.

He has performed medical research and clinical work at the University of Louisville School of Medicine, Kansas University Medical Center, and while serving as a reproductive endocrinologist for the U.S. Navy.

Dr. Corley's research has been published in medical journals and in medical books. He also has taught at the Medical University of South Carolina, at the University of Louisville School of Medicine, and at the University of Kansas School of Medicine.

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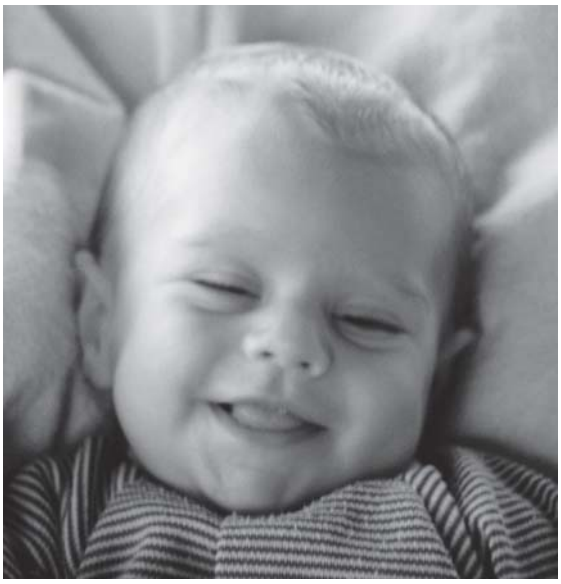

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Conceptions is published quarterly for a select group of OB/GYNs and their patients. To receive extra copies of the newsletter or to be placed on our mailing list, please call Carla Scott at **(856) 988-0072** or e-mail her at: **info@startfertility.com.**

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Happy Birthday to . . .

Averi McKenna Cooper, born on June 21, 2003, to Lynne and Kevin Cooper.
Ewan Brasure Wickward, born on December 6, 2003, to Shawn and Robert Wickward.
Alysa Bralow and **Devon Bralow**, born on January 20, 2004, to Jennifer and Ian Bralow.
Connor Joseph Wharton, born on February 1, 2004, to Tracy and Steve Wharton.
Christopher James Kazunas, born on February 26, 2004, to Lisa and Stephen Kazunas.
Lucas John Knoop, born on March 25, 2004, to Laura and John Knoop.
Olivia Rose Favilla, born on April 4, 2004, to Dan and Donna Favilla.
Christopher Briggs, Brandon Briggs, and **Andrew Briggs**, born on April 14, 2004, to Christina and Jeff Briggs.
Madison Kate Duenas and **Kayla Nicole Duenas**, born on May 10, 2004, to Laura and Maurice Duenas.
Victoria Mary Santoro, born on June 3, 2004, to Angela Santoro.
Griffin Edward Gaughan, born on June 7, 2004, to Cynthia Sara and Vincent Gaughan.

All the babies and parents are doing well. Thank you, DVIF&G!

DVIF&G Recognized for Quality Laboratory Services

DVIF&G's Reproductive Laboratories have met all criteria for Laboratory Accreditation by COLA, a national healthcare accreditation organization. Accreditation is given only to laboratories that apply rigid standards of quality in day-to-day operations, demonstrate continued accuracy in the performance of proficiency testing, and pass a rigorous on-site-laboratory survey. The DVIF&G laboratories have earned COLA accreditation as a result of a long-term commitment to provide quality service to its patients. COLA is approved by the federal government and sponsored by the American Academy of Family Physicians, the American Medical Association, the College of American Pathologists, and the American Osteopathic Association.