# Sometimes the Journey to Parenthood Needs a Technology Nudge

New technologies and procedures help tackle infertility.

## Introduction

The birth of a baby is one of nature's many wonders. With more than 250 babies born in the world every minute, it would appear to be a commonplace event[1]. Yet, there is nothing ordinary or routine about conceiving a child for the more than 70 million infertile couples worldwide. Since the first test tube baby was born in 1978, significant progress has been made in the treatment of infertility. Assisted reproductive technologies (ART) enable thousands of infertile couples to have a child.

It's not surprising that ART is the acronym for these procedures. When nature can't complete the task, it takes a mixture of talent, skill, and technology to finesse an egg and sperm to form an embryo. It's what attracted Angeline Beltsos, MD to reproductive endocrinology. "After looking at other fields, including engineering, I decided to go with a profession with more of a human touch," Dr. Beltsos said. "As a medical student, I had the opportunity to work with a prominent reproductive endocrinologist and decided that was the specialty for me. Delivering babies is amazing. Helping couples conceive adds something very special to the experience."

After completing a Reproductive Endocrinology and Infertility fellowship in 1997, Dr. Beltsos began her career in private practice. In 2000, she joined the Fertility Centers of Illinois (FCI), where she is Co-Managing Partner, and Director of Research and Education, and Business Development.

"Reproductive endocrinology is a field that's changing rapidly as new methods and technologies are developed," Dr. Beltsos added. One of the latest additions is next-generation sequencing (NGS)-based pre-implantation genetic screening (PGS). These tests are used to screen embryos or eggs for chromosome aneuploidy (an abnormal number of chromosomes), a major cause of *in vitro* fertilization (IVF) failure[2,3]. The risk of aneuploidy rises with a mother's age, increasing the chance of miscarriage and decreasing the pregnancy rates for women in their late 30s and early 40s[4].

iCommunity spoke to Dr. Beltsos about the field of reproductive endocrinology and the technological advances assisting infertile couples in their pursuit to have a baby.

**Angeline Beltsos, MD,** is Co-Managing Partner, and Director of Research and Education, and Business Development at Fertility Centers of Illinois (FCI).

Q: When was FCI founded and how has it grown over the years?

Angeline Beltsos (AB): FCI offers comprehensive medical and infertility services and was founded in the late 1990s by a group of reproductive endocrinologists who decided to merge their practices. It allowed FCI to increase efficiencies through the sharing of resources and to grow more quickly. We now have one of the larger U.S. practices, with 10 offices, 2 IVF laboratories, and 11 physicians. We perform approximately 3000–4000 IVF cycles a year.

Q: What factors are contributing to FCI's growth?

AB: One of the factors increasing the need for fertility treatment is age. In general, the number of infertile women seeking help in becoming pregnant is increasing because people are waiting longer to have children. Women are getting married later in life, and many married couples are waiting to reach financial stability before starting a family. Many of our patients are over 35-years old.

In some states like Illinois, many of our patients have medical insurance that covers IVF costs. Yet, lack of insurance isn't a hurdle for most people. We have a significant number of U.S. patients who travel hundreds of miles to Chicago for care even though they don't have insurance. We also have international patients that are traveling half way around the world to our facilities.

Q: What's your role at FCI?

AB: My primary role is as a physician. I'm a member of an 11-physician team that practices well together, and that's been an important part of our success. In addition, I'm a managing partner at FCI and Medical Director of the practice.

I'm also in charge of FCI Research and Education. We're involved in clinical trials of new methods and technologies. OBGYN residents in the Chicago area rotate through our offices, obtaining experience with various reproductive cases. As the Chair of the Midwestern Reproductive Symposium that FCI started 11 years ago, I'm involved in continuing medical education program development for physicians, nurses, allied health professionals, and scientists practicing or conducting research in reproductive medicine.

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Q: How have the procedures and tools that you use to help people conceive changed since you entered the field in the mid-1990s?

AB: When I was a medical student, we were mainly performing GIFT and ZIFT procedures. IVF was less prevalent and egg retrievals were done mostly laparoscopically, and not with transvaginal ultrasound. Today, it would be unusual to utilize these techniques, except in rare cases.

Another change is the increasing popularity of third-party reproduction, which has resulted in more patients achieving pregnancies with egg donors and surrogacy. Furthermore, we now use a process called vitrification to freeze eggs and embryos that enables higher survival rates than a slow-freeze process.

IVF methods have progressed as well, with the push to wait until day 5 blastocyst culture for embryo transfer instead of waiting only 2 or 3 days. When the embryo begins to turn into a blastocyst, it blossoms and expands. A growing number of practices, including ours, are now waiting for day 5 blastocyst cultures to improve transfer success. In fact, getting to the optimal blastocyst stage might require us to wait until day 5, 6, or 7.

Finally, the development of PGS and trophectoderm biopsy provides us with a more effective way of screening embryos for genetic health. It's been a tremendous addition to our field.

Q: What's your experience with PGS and how has it changed the way you perform IVF cycles?

AB: In PGS's earliest days, FCI worked closely with industry pioneer Dr. Yury Verlinsky. He developed some of the very first PGS procedures in the United States.

Over the years, we've used a number of procedures to screen embryos. We began with single-gene testing and then moved on to aneuploidy screening using FISH and polar body biopsy techniques developed by Dr. Verlinsky. We later shifted to blastomere biopsying of the day 3 embryo, and now perform blastocyst trophectoderm biopsies day 5, 6, or 7. With older techniques such as fluorescence *in situ* hybridization (FISH), there is a higher margin of subjectivity, because you're reading the colored probes that aren't always clear and possible misrepresentation of missing or adding chromosomes.

We now routinely perform trophectoderm biopsy and use the 24sure® assay or VeriSeq™ PGS to screen the chromosomes for aneuploidy. Both offer a significant improvement over FISH, which can screen only a limited number of chromosomes. PGS has become a powerful tool, enabling us to help couples have healthy pregnancies.

Q: Is FISH still used in some clinics?

AB: FISH is used in certain medical situations, but many clinics that have an active PGS program now screen all 24 chromosomes using single nucleotide polymorphism (SNP) microarrays, comparative genomic hybridization (aCGH) microarrays such as 24sure, NGS using VeriSeq PGS kits and the MiSeq® System, or rapid quantitative fluorescent PCR (qtPCR). These tests are very useful in patients with advanced maternal age. We're hoping in the future that they will help us understand the reasons behind miscarriage and unravel the mysteries of recurrent pregnancy loss.

> "A growing number of practices, including ours, are now waiting for day 5 blastocyst cultures to improve transfer success."

Q: Why is the blastocyst stage the optimal stage for embryo biopsy?

AB: The risk of damage to the embryo is less when we biopsy at the more developed blastocyst stage. When you biopsy a day 3 embryo, its ability to turn into a blastocyst, successfully attach to the uterine lining, and advance in development might be compromised. A trophectoderm biopsy at day 5–7 enables us to obtain a few more cells in the biopsy. It provides us with more DNA to perform PGS on the sample.

Q: How much DNA do you need to perform PGS?
AB: We can run the 24sure assay using DNA from just one cell. The VeriSeq NGS-based assay is a more advanced method, providing results within 12 hours. With VeriSeq PGS, many samples can be analyzed simultaneously at high throughput, which is more efficient and economical. The impact of NGS on our field and medicine in general has been revolutionary.

> "We now routinely perform trophectoderm biopsy and use the 24sure assay or VeriSeq PGS to screen the chromosomes for aneuploidy."

Q: How experienced are your IVF lab personnel?
AB: We're very lucky to have talented and experienced scientists and embryologists working in our IVF lab. They are masters of the simpler methods, such as intracytoplasmic sperm injection (ICSI) and assisted hatching, and the more intricate vitrification techniques for freezing and thawing embryos and eggs. We have a strong embryo vitrification program and have a 95–98% embryo survival rate. Their high performance level and skill enhances our pregnancy success rates. Our IVF lab team is well-recognized and teaches trophectoderm biopsy techniques to people from all over the world.

Q: What percentage of your embryo transfers are with frozen versus fresh embryos?
AB: Today, 50% of our embryo transfers are with frozen embryos. We're trying to get patients more comfortable with frozen IVF cycles. There will always be some patients who, for various reasons, might want to do a fresh cycle. For example, they might already be in the midst of taking fertility drugs and prefer to have us implant a fresh embryo. There is a cost for freezing embryos and the need for taking a whole new set of medicine.

While performing fresh embryo transfers sounds natural, the uterus isn't really ready for pregnancy. It's been hyperstimulated by the drugs that support egg production, such as GnRH agonists. Work from Dr. Paul DeVroey's lab at the Vrije Universiteit Brussels has shown that hyperstimulation disrupts the calm, normal uterine environment as it prepares for the embryo[5]. It impacts uterine stickiness, negatively impacting the ability of the fresh embryo to attach to the uterine lining. Research studies by our team, Dr. Bruce Shapiro at The Fertility Center of Las Vegas, and Dr. Ernesto Bosch at IVI in Spain show that hyperstimulation also causes a premature rise in progesterone that cuts the chance of pregnancy in half[6,7]. We can use drugs to decrease ovarian hyperstimulation, but those often have a negative effect on the uterine cavity. The uterus is key to pregnancy success, with uterine lining tissue genotyping studies showing a profound difference between the hyperstimulated and normal uterine environment at day 6. Yet, the embryo cannot be transferred too late on day 6 because the uterine lining rapidly loses its stickiness, lessening the chance of implantation. Transplanting the fresh embryos too late might mean that everyone's hard work will be for naught. There's also a shorter window of opportunity when transplanting fresh embryos. It requires PGS to be performed overnight, with the screened embryos transplanted on day 6.

Embryo vitrification freezes the embryo without crystallizing and fracturing the cellular equipment important for its viability. We have found that if the embryo survives the vitrification process, it works as well as a fresh embryo, even though it might have been frozen for a day or for years. It enables us to delay implantation by at least a month. After 30 days, the uterine lining has shed, presenting a calm environment for the embryo that supports successful implantation. Our data shows that the frozen embryo transfer method potentially doubles the pregnancy rate[8].

> "With VeriSeq PGS, many samples can be analyzed simultaneously at high throughput, which is more efficient and economical."

Q: When do you talk to patients about the benefits of PGS?
AB: I bring it up when we're going over the IVF process. I want them to know that no matter what their situation, this technology exists and is an option for them.

The IVF discussion begins with the process of growing the embryos to the day 5 stage. We review the possibility that we might need to perform a couple of egg retrievals and bank several day 5 embryos just in case they are a poor responder and we need to introduce more than one embryo into the uterus. We also discuss the fee to perform PGS. We'll combine that data with each embryo's morphology and pick the best embryo for transfer.

PGS also offers significant benefits to someone who has miscarried in the past [recurrent pregnancy loss (RPL)], or is over 40 years old and has a higher risk of miscarriage. Especially with women at the precarious age of 40, time is not their friend. We'll discuss the fact that it takes time to heal after a miscarriage and with each passing day, her chances of becoming pregnant lessen. PGS can eliminate the time wasted on an embryo that is aneuploid and never destined to become a baby. Though the cost of PGS is real, there are

also costly and important implications for older women if it's not performed.

Some women are concerned about multiple births. There is a movement in the United States and globally towards elective single embryo transfer. Patients and insurance companies like the idea that PGS enables us to select the one best embryo, avoiding the risk of multiple births of twins, triplets, or more.

> "The impact of NGS on our field and medicine in general has been revolutionary."

Q: What is the percentage of women who choose to have PGS of their embryos?
AB: About 10–30% of my patients choose to have PGS today. I see that percentage growing, as more people learn about it. Many people are surprised that such a technology exists, even doctors and nurses. I think the use of PGS will become commonplace as more women discuss it within infertility support groups and share how it's led to their successful pregnancies.

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### Glossary

Blastocyst - Early stage of an embryo, typically 5 days following fertilization; consists of a cavity, an inner cell mass, and an outer trophectoderm.

GIFT – Eggs and sperm are mixed before insertion into the fallopian tubes where fertilization can take place in the body.

ICSI – A variation of IVF in which the sperm is injected directly into the oocyte cytoplasm.

IVF – Fertilization of the egg by sperm in a petri dish, outside of the human body.

Oocyte - The female germ cell involved in reproduction that contains half the diploid number of chromosomes (haploid); also known as an egg cell

Preimplantation genetic screening (PGS) – Screening embryos or oocytes for the correct number and type of chromosomes; PGS does not look for a specific genetic disorder.

Trophectoderm – The outer layer of cells (adjacent to the zona pellucida) that forms a flat squamous epithelial layer of cells. Following blastocyst hatching, the trophoblast layer is involved with initial adhesion to the uterine wall and subsequent implantation within the wall.

Vitrification - A quick-freezing method used to preserve eggs and embryos allowing an egg taken in one cycle to be implanted in another.

ZIFT - Fertilized egg are inserted into the fallopian tubes within 24 hours of fertilization.

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