

The Female Patient[®]

APRIL 2010 | VOL. 35, NO. 4

www.femalepatient.com

Endometriosis in Adolescents *page 17*

**Ovarian Cancer
Early Detection** *page 22*

**IVF Then and Now,
30 Years Later: Best Practices
in Reproductive Medicine** *page 27*

**Robot-Assisted Laparoscopic
Sacrococpopexy** *page 33*

**Dietary Clinical Trials
of the WHI: Part 2** *page 39*

**Male Perspective on
Emergency Contraception** *page 43*

**Sleep Deprivation
and the Obstetrician** *page 46*

**Online Patient
Communication** *page 51*


**HPV DNA Co-Testing
Adoption** *page 53*

Patient Handout
**What You Should Know
About Endometriosis**



facebook **twitter**

Become a fan of *The Female Patient* and
The Buzz on Bioidenticals on Facebook
and follow us on Twitter.

A photograph of the Golden Gate Bridge in San Francisco, California, viewed from a low angle looking up at the bridge's structure against a clear blue sky. The bridge's towers and suspension cables are prominent, and the water of the bay is visible at the bottom.

Be sure to visit

The Female Patient

at

**Booth
1115**

at the

ACOG
**58th Annual
Clinical Meeting**

May 15 to 19, 2010

San Francisco

The
**Female
Patient**

IVF Then and Now, 30 Years Later: Best Practices in Reproductive Medicine, Part 1

Mark P. Trolice, MD

Common Clinical Scenario: A 29-year-old white female and her partner of the same race present with 2 years of infertility. Her husband experienced infertility in a prior marriage, with the diagnosis of azoospermia, but did not pursue further evaluation. They are not interested in therapeutic donor sperm insemination. The patient also would like information on fertility preservation options because she is concerned about her age. You refer the male to a urologist, who diagnoses congenital bilateral absence of the vas deferens with otherwise normal external male genitalia. Astute testing determines both the male and female are carriers of cystic fibrosis.

What fertility treatment options using the male partner's sperm are available to this couple? How can they avoid the potential transmission of cystic fibrosis to their offspring? Are there any fertility-sparing options available today?

The first of this 2-part series will present the milestones of in vitro fertilization (IVF) from its foundation to intracytoplasmic sperm injection, blastocyst culture, and third-party reproduction. Part 2 will examine preimplantation genetic diagnosis and discuss the new technologies of egg freezing, comparative genome hybridization, and metabolomics. This

Mark P. Trolice, MD, is Director, Fertility CARE (Center of Assisted Reproduction & Endocrinology); and Founder, Fertile Dreams, Inc; both in Orlando, FL. He is also on the Editorial Board of *The Female Patient*.

review article will help health care professionals understand the evolving science of advanced reproductive technology, appropriately counsel patients, and provide treatment options.

Since the first baby born in 1978 from a “natural cycle” IVF treatment (ie, without ovary-stimulating medications), the field of reproductive medicine has been simultaneously associated with cutting edge science and political/social/religious controversy. The technology was catapulted to the forefront of reproductive endocrinology, offering patients unprecedented opportunity for parenting when adoption previously was the only alternative. The moral dilemma of the time was concern over engineering babies and “playing God.”

Thirty years later, the number of live births from the use of IVF in the United States is approximately 1% (Figure 1).¹ There are many new answers to patient infertility problems, but just as many, if not more, questions raised over the applicability of this never-ending new frontier. Ultimately, this begs the question: Just because a procedure *can* be performed, *should* it? Hence, the enduring slippery slope that is medically assisted reproduction.

IVF BASICS

The basic premise of IVF involves controlled ovarian hyperstimulation (COH) in order to obtain multiple oocytes from a single follicular phase. In a natural cycle, hundreds of antral follicles undergo gonadotropin-dependent stimulation, yet only one dominant follicular cyst expels an oocyte during the 50-hour luteinizing hormone (LH) surge; the remaining cohort of

FOCUSPOINT

Just because a procedure *can* be performed, *should* it? Hence, the enduring slippery slope that is medically assisted reproduction.



“I’m Sure.”

Let’s talk Essure

The in-office solution for permanent birth control

Proven - 7+ years of commercial data, ~400,000 procedures, 200+ publications

Highly effective - 99.74% efficacy rate at 5-year follow-up*

Easy - Micro-insert placed transcervically in an office setting

High patient satisfaction - No incisions, no hormones, no slowing down

Conceptus[®] Inc.

essure[®]

YOUR FAMILY IS COMPLETE.
YOUR CHOICE IS CLEARSM

www.essuremd.com

Indications for use: The Essure procedure is used for women who desire permanent birth control (female sterilization) by bilateral occlusion of the fallopian tubes. **Contraindications:** If a patient is uncertain about her desire to end fertility; pregnant; has terminated or delivered less than 6 weeks before the Essure procedure; has an active or recent upper or lower pelvic infection. **Warnings:** The Essure procedure is not reversible, and is not suitable for all women. **Cautions:** Federal law restricts this device to sale by or on the order of a physician; should only be used by physicians who are knowledgeable hysteroscopists and have successfully completed the Essure training program. For a complete description of cautions, warnings, potential adverse events and contraindications see the Essure System Instructions for Use. *The five-year effectiveness was demonstrated in a portion of the women undergoing clinical studies. There continue to be no pregnancies to date among patients who had been enrolled in the Essure phase II and pivotal trials. ©2010 All rights reserved. Conceptus and Essure are registered trademarks and Your Family Is Complete Your Choice Is Clear is a service mark of Conceptus, Inc. CC-1945 10FEB10F

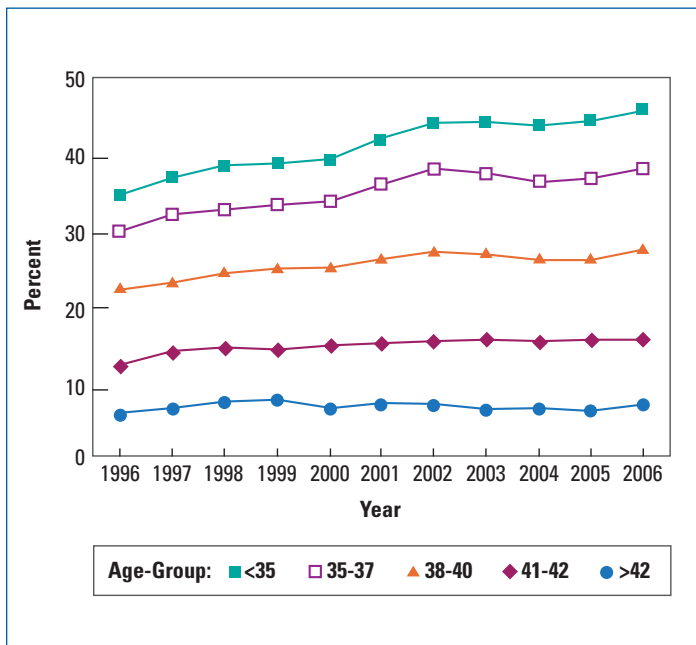


FIGURE 2. Percentages of transfers that resulted in live births for assisted reproductive technology cycles using fresh nondonor eggs or embryos, by woman's age, 1996-2006.

Source: www.cdc.gov/ART/ART2006/section5.htm.

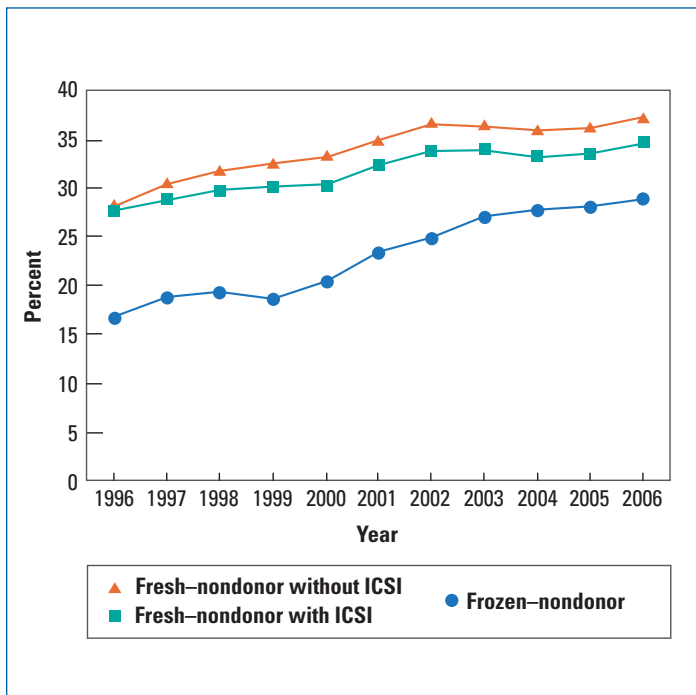


FIGURE 3. Percentages of transfers that resulted in live births using fresh or frozen nondonor eggs or embryos, by intracytoplasmic sperm injection (ICSI), 1996-2006.

Source: www.cdc.gov/ART/ART2006/section5.htm.

otropin-releasing hormone (GnRH) agonists were added for hypothalamic-pituitary-ovarian (HPO) suppression, and this remains the standard today. Described as the “long protocol,” the GnRH agonist is usually begun in the mid-luteal phase, either one week after spontaneous ovulation or overlapping combined oral contraceptives. Within 8 days, HPO suppression ensues (medical menopause) and effective ovulation inhibition is the rule with rare exception.

Because of the extended duration of injections and increased risk of ovarian hyperstimulation syndrome with GnRH agonists, an alternative became available in the late 1990s in the form of GnRH antagonists. The main advantage of this new option is its mid-follicular initiation timing in the treatment cycle. This results in immediate and reversible suppression of ovulation, with overall fewer days of injections. The prompt cessation of ovulation suppression with the antagonists has allowed for final maturation of the oocytes with GnRH agonists to reduce the risk of ovarian hyperstimulation syndrome in hyperresponding patients. This process avoids the hCG trigger, a known putative stimulus for this serious complication, but luteal support and outcome may be compromised.⁶ To date, there remain lingering concerns of efficacy with the antagonists compared to the agonist.

FERTILIZATION: AVOIDING DONOR SPERM

The assisted fertilization technique of intracytoplasmic sperm injection utilized during IVF revolutionized the treatment of male factor infertility when used for azoospermia (sperm produced in very low numbers or entirely absent from ejaculation). Serendipitously discovered in 1992, intracytoplasmic sperm injection resulted from the insertion of a single sperm directly into the ooplasm of the oocyte rather than just under the zona pellucida (the intended destination).⁷ Some men experience azoospermia from absent or blocked reproductive ducts (obstructive), whereas others may have no sperm production with normal anatomy (nonobstructive). A minor outpatient procedure, testicular sperm aspiration, harvests sperm directly from the testes and is then used with IVF and intracytoplasmic sperm injection. Of men with congenital bilateral absence of the vas deferens, 42% to 72% are carriers of cystic fibrosis and require testicular sperm aspiration.^{8,9}

Originally regarded as experimental, intracytoplasmic sperm injection was thrust into IVF clinic procedures without the usual random-

Video of Intracytoplasmic Sperm Injection

Access this video on the technique of intracytoplasmic sperm injection, and see a single sperm taken up into a micropipette and be inserted directly into a single egg to overcome a male factor. Windows Media Video (WMV) format (549 kb) http://myfertilitycare.com/ivf_icsi.asp.

ized prospective trials and safety analysis. Despite its clear efficacy, concerns remain regarding the genetic implications of this technology, as will be discussed in Part 2 of this article, and more recently a reduction in the male sex ratio.¹⁰ Pregnancy rates are analogous with or without the use of intracytoplasmic sperm injection (Figure 3).

BLASTOCYST DEVELOPMENT: ADVANCED EMBRYO CULTURE

Until the later 1990s, following fertilization the embryos were routinely grown and transferred on day 2 (2-4 embryo cell stage) or day 3 (6-8 embryo cell stage), yet implantation rates were only 10%.¹¹ Methodology in the laboratory required understanding more complicated metabolic requirements of the embryo at this early stage. From fertilization until day 3, the oocyte DNA is believed to contribute to embryo development, then the embryonic genome orchestrates further growth. The ability to culture embryos to the blastocyst stage created several advantages in IVF, namely improved implantation and reduced number of embryos transferred. A blastocyst is formed when an embryo reaches the 5- to 7-day stage, and the embryo has between 60 and 100 cells distributed in 2

areas: an outer trophoblast (which will later form the placenta) and an inner cell mass (which will later become the fetus). Initially, the pregnancy success following day 3 versus day 5 embryo transfer did not appear to differ.¹² However, recent advances in chronic gonadotropin hormone and metabolomics are promising to further enhance the high implantation potential of a single blastocyst, thereby lowering the multiple gestation risk.

COMPLICATIONS

Of the side effects and risks involved with infertility treatment, the most severe and feared is ovarian hyperstimulation syndrome.¹³ The reproductive pathophysiologic equivalent of severe preeclampsia, severe ovarian hyperstimulation syndrome occurs in 0.2% to 0.5% of treatment cycles and originates from excessive follicular response by the ovaries to gonadotropin injections, causing vascular permeability, ascites, and hemoconcentration that result in prerenal azotemia, thromboembolism, pulmonary compromise, and, rarely, mortality.^{14,15} Patients at higher risk for ovarian hyperstimulation syndrome are those with a prior history and with polycystic ovary syndrome. Treatment strategies at preventing this life-threatening condition have included:

- Intravenous albumin
- Discontinuation of gonadotropin injections (called "coasting") until the estradiol level falls to a more acceptable level (usually 3,000 pg/mL)
- Cryopreservation of all the embryos and avoiding embryo transfer
- Triggering the final maturation of eggs with a GnRH agonist rather than hCG
- The dopamine agonist cabergoline.

All of these methods have met with varying degrees of success, but the only foolproof method is cancellation of the cycle prior to hCG injection. Though the exact etiology has not been elucidated, ovarian hyperstimulation syndrome invariably results from hCG stimulation to the ovarian follicles in conjunction with vascular endothelial growth factor activation. Consequentially, the hCG trigger

FOCUSPOINT

Of the side effects and risks involved with infertility treatment, the most severe and feared is ovarian hyperstimulation syndrome.

More Information About IVF

To review the 2009 World Health Organization glossary of IVF terms, see: Zegers-Hochschild F, Adamson GD, de Mouzon J, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. *Fertil Steril*. 2009;92(5):1520-1524.

Interested in a more detailed history of in vitro fertilization? Access "The History of IVF: The Milestones," a 30-year timeline, at www.ivf-worldwide.com/ivf-history.html.