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## The state of ART

By Mark P. Trolice, MD, FACOG, FACS, FACE

*As the use of assisted reproductive technologies increases worldwide, referring clinicians need to understand the rapid advances in this field to appropriately counsel infertile patients.*

Since 1978, hundreds of thousands of babies have successfully been born in the United States because of assisted reproductive technologies (ART), most commonly in vitro fertilization (IVF).<sup>1</sup> Although initially modest, pregnancy rates using IVF now exceed the natural fecundity of couples for women younger than 35 years of age.<sup>2</sup> Despite lingering studies that suggest a possible association with birth defects,<sup>3</sup> IVF remains the most effective method of treating infertility.

This article will look at the state of ART as summarized in the latest report provided by the Centers for Disease Control and Prevention (CDC) as part of the Fertility Clinic Success Rate and Certification Act of 1992 that requires the Department of Health and Human Services, through the CDC, to develop a model program for the certification of embryo laboratories, which is carried out voluntarily by interested states.<sup>1</sup> The Society of Assisted Reproductive Technology (SART) assists IVF clinics in data collection to report to the CDC and to comply with the 1992 act; alternately, clinics may report directly to the CDC. Because the CDC performs an extensive and time-consuming verification process and includes in its analysis fertility clinics that had not reported to SART, the CDC results are delayed in being released to the public. More current SART statistics can be found online ([www.sart.org/find\\_frm.html](http://www.sart.org/find_frm.html)).

### Success rates by age

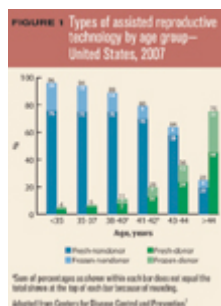


Figure 1: Types of assisted reproductive technology by age group—United States, 2007

In 1996, nearly 60,000 IVF cycles were performed nationally; nearly 140,000 cycles were started in 2006.<sup>1</sup> A review of CDC data of ART cycles by age group shows an increased use of egg donation in the later reproductive years, as expected (Figure 1).<sup>1</sup> Approximately 40% of women who underwent IVF were younger than age 35 years, and 20% were older than 40 years (Figure

2).<sup>1</sup> Of the 11% of cycles discontinued before egg retrieval, approximately 84% were because of poor or no egg production. Donor eggs (fresh and frozen) comprised the rest of the cycles. Less than 1% of cycles used a now-antiquated gamete or zygote intrafallopian transfer that requires laparoscopy for egg retrieval and/or transfer. Clinic size as reflected by the number of IVF cycles has no influence on IVF outcome.

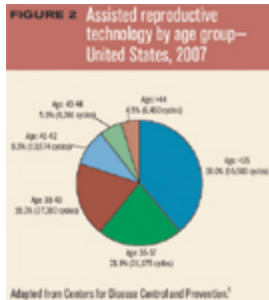


Figure 2: Assisted reproductive technology by age group—United States, 2007

Accounting for 1% of all live births in the country, IVF outcome measures of success are presented in various ways.<sup>4</sup> The most meaningful statistic, however, is the percentage of live births per embryo transfer (LB/ET), which equals 35% of all cycles.<sup>1</sup> This number represents the chance of pregnancy for a woman after ovarian stimulation, egg retrieval, and embryo transfer. Some cycles do not proceed to a fresh embryo transfer, in contrast to frozen, because of rare problems such as ovarian hyperstimulation syndrome, fluid noted in the uterine cavity, or failed fertilization of eggs. Consequently, the LB/ET rate is usually slightly higher than the LB/egg-retrieval rate. A prior live birth conceived naturally or by ART modestly increases the success rate with IVF. A prior unsuccessful IVF cycle slightly decreases the success rate in the subsequent cycle. A history of miscarriage has no significant influence on IVF outcome.

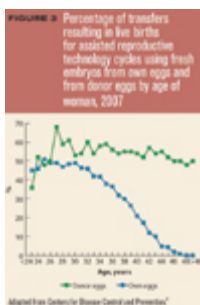


Figure 3: Percentage of transfers resulting in live births for assisted reproductive technology cycles using fresh embryos from own eggs and from donor eggs by age of woman, 2007

Live birth rates from IVF remain relatively constant until age 32 to 33 years, when there begins a gradual and steady decrease because of declining ovarian reserve (DOR; Figure 3).<sup>1</sup> Consequently, the live birth rate declines so that approximately only 5% to 10% of women aged

40 to 43 years will have a live birth from IVF per cycle; the rate in women aged 43 and older (using their own eggs and not a donor's) is less than 5%.

Although there is no age precluding the chance of success, egg donation offers a dramatically higher live birth rate in women 40 years of age and older. Chromosomally abnormal embryos that result from DOR may cause a steep rise in the rate of miscarriages for women in their late 30s, approaching 50% for women in their 40s.

### **Complications and multiple births**

Complications from IVF pregnancies are classified as any outcome other than a single healthy live birth at term. Offering reassurance, the miscarriage rate after an IVF cycle is 16% and consistent with the natural rate.<sup>1</sup> Less than 5% of pregnancies implant outside the uterus (ectopic pregnancies) and usually occur in patients with tubal disease, possibly caused by the affected fallopian tubes secreting an embryo- or endometrial-toxic factor, thereby decreasing intrauterine implantation and/or acting as a chemoattractant for the embryo.<sup>5</sup> As a result from ART, a pregnancy coincidentally occurring in the uterus and fallopian tube occurs in 1% of cycles,<sup>6-8</sup> much higher than the natural estimated rate of 1 in 7,963 to 1 in 30,000 pregnancies.<sup>7,8</sup> Although declining, the percentage of multiple gestations (nearly 32%) from ART cycles far exceeds the natural occurrence (1%-2%).<sup>4</sup> The rate of high-order multiple births from IVF (ie, triplets or more) is 6% and has continued to decline over the last decade in response to American Society for Reproductive Medicine/SART guidelines first released in 2006 and then updated in 2008 and 2009.<sup>9</sup>

More recent revisions on embryo transfer guidelines have been prompted by the notoriety of the "Octomom," the American woman who gave birth to octuplets in January 2009. These guidelines recognize the decline in fertility as a woman ages, therefore allowing for more embryos to be transferred in the later reproductive years. In 2007, the practice of reducing multiple gestations by limiting the number of embryos transferred is shown by 46% of transfers resulting in only 2 embryos returned to the uterus.<sup>10</sup> Only 11% and 28% of transfers involved 1 and 3 embryos, respectively.

Because the majority of embryo transfers occur 3 days after egg retrieval (64%), there appears to be no difference in pregnancy rate or multiple births when comparing 2 versus 3 embryos transferred. Across all ages, pregnancy rates are higher when embryos are transferred on day 5 at the blastocyst stage, but multiple-infant live births increase from 29% to 35% compared with day-3 transfers.<sup>1</sup> Unless the number of viable embryos available to transfer on day 3 are consistent with SART guidelines, most clinics will maintain the embryos in the laboratory culture until the blastocyst stage for transfer in order to benefit from natural selection and an improved implantation rate.<sup>10</sup>

The incidence of monozygotic twinning (MZT) after ART cycles is 0.9% (0.8%-0.9%) compared with 0.4% in natural conceptions.<sup>11</sup> Blastocyst transfer and intracytoplasmic sperm injection (ICSI) are associated with 4.25 and 2.25 times higher risk of monozygotic twins, respectively. The prevailing theory for MZT after ART is a breach in the zona pellucida (shell structure) of the embryo, such as through assisted hatching or ICSI.<sup>12</sup> Yet, the additional micromanipulation through the zona for blastomere cell biopsy and preimplantation genetic diagnosis (PGD), even during ICSI treatment, does not appear to increase MZ twinning compared with non-PGD ICSI cycles.<sup>13</sup>

Although blastocyst transfer alone does not breach the zona, the exact mechanism responsible for increased risk of MZT has not been elucidated, but speculation includes effects on the embryo from prolonged in vitro culture systems and the experience of the embryologist.<sup>14</sup>

### **Incidence of preterm birth**

The IVF preterm birth rate of 12.5% is similar to the natural rate of 12.8%,<sup>4</sup> and the rate increases dramatically with the number of fetuses—63% in twins and 95% in triplets or more.<sup>1</sup> Preterm births occur in 18.5% of singleton births when the pregnancy initially began with multiple fetuses. A debatable theory for this is the effect from the initial number of embryo implantations taking precedence over the final number of fetuses during the pregnancy with regard to duration of gestation. Although the uterine "memory" has been suggested as a mechanism in multifetal reduction outcomes, it has also been opposed.<sup>15,16</sup>

### **Intracytoplasmic sperm injection technology**

A revolutionary advance in male infertility was discovered in the 1990s with ICSI, whereby a single sperm pierces the oocyte cell membrane by micromanipulation in order to overcome sperm dysfunction and fertilize the egg.<sup>17</sup> In 2007, 52% of IVF cycles used ICSI without a diagnosis of male factor, suggesting overzealous use of this technology.<sup>1</sup> When comparing ICSI with conventional fertilization, outcomes of success are equivalent. Paradoxically, without a diagnosis of male factor, use of ICSI resulted in a lower rate of success.

### **Frozen and donated embryo transfers**

Frozen embryo transfers are less likely to be successful compared with fresh transfers. In women using their own eggs, LB/ET is 29%, with a lower multiple-infant live birth rate of 24%.<sup>1</sup> Some women elect to use frozen embryos donated from other couples, in which case the LB/ET is 32%.

An increasingly appreciated option is the use of embryo donation (ED; ie, supernumerary embryos donated from infertility patients who had undergone IVF). Although not reported by SART, ED success rates should be comparable to frozen embryo transfers and strongly influenced by the age of the donating female. Although the biologic relation is sacrificed, ED is less costly than its fresh IVF counterparts and allows the patient to realize a pregnancy.

Although age-related decline in fertility is well established in women using their own eggs, donor egg cycles avoid this influence.<sup>18</sup> Success rates for women in their 40s and 50s receiving donor eggs are comparable to younger women, presumably because the uterus maintains implantation potential with advancing age.<sup>19</sup> The LB/ET in fresh egg-donation cycles is 54%, with 38% resulting in multiple-infant live births.<sup>1</sup> In frozen cycles, LB/ET is 32%.

### **Preimplantation genetic diagnosis**

Since 1990, embryo biopsy and PGD has offered patients who are carriers of a disease (eg, cystic fibrosis and sickle cell anemia) the ability for single-gene defect screening to avoid transmission to a child. Although not specifically included in reporting statistics to the CDC, PGD cases appear to have a lower pregnancy rate, presumably from selection of the disease trait limiting numbers of embryos available to transfer.<sup>20</sup> Recent advances in entire karyotyping of the embryo through comparative genome hybridization (CGH) and microarray show the promise of increasing embryo implantation rates and reducing miscarriage.

## **New horizons**

More than 30 years ago, the first baby was born by a natural cycle of IVF. In the time since this remarkable accomplishment, ART has evolved rapidly to allow couples the ability to freeze extra embryos from the initial stimulating cycle for later use, fertilize eggs through testicular sperm retrieval and ICSI, develop embryos to the blastocyst stage with refined laboratory culture systems, biopsy embryos through PGD for single-gene defects to avoid transmission of disease, donate eggs to a patient or surrogate, freeze eggs for fertility preservation in cancer patients, and, most recently, analyze the karyotype of embryos through CGH and microarray to potentially reduce miscarriage and improve pregnancy rates, particularly in the later reproductive years of women.

Although concerns linger regarding the possible association with birth defects, and the risk of multiple gestations remains a paralyzing focus on the field, ART has allowed hundreds of thousands of patients who would otherwise be childless or who would have only the option to adopt to build a family. The enduring goal is to use the least amount of medication and embryos transferred in order to maximize the chances of giving birth to a single, live, healthy child.

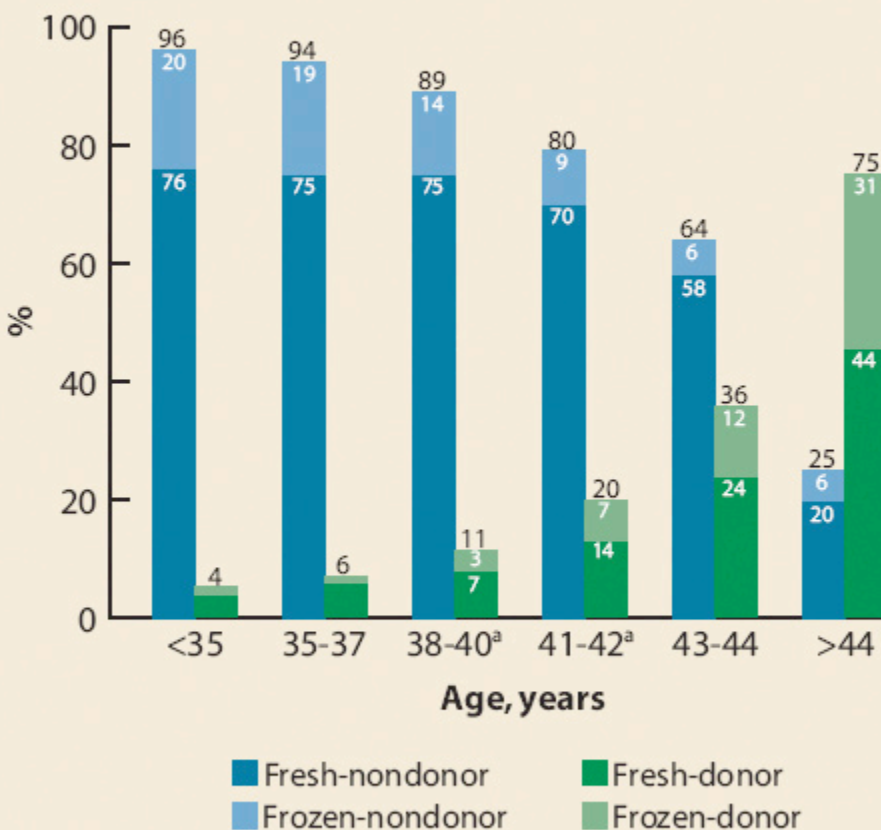
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## **REFERENCES**

1. US Dept of Health and Human Services, Centers for Disease Control and Prevention; American Society for Reproductive Medicine; Society for Assisted Reproductive Technology. *Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports 2007*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2009.
2. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *New Engl J Med*. 1995;333(23):1517-1521.
3. Reefhuis J, Honein MA, Schieve LA, Correa A, Hobbs CA, Rasmussen SA; National Birth Defects Prevention Study. Assisted reproductive technology and major structural birth defects in the United States. *Hum Reprod*. 2009;24(2):360-366.
4. Martin JA, Hamilton BE, Sutton PD, et al. *Births: Final Data for 2006. National Vital Statistics Reports*. Vol 57. No 7. Hyattsville, MD: National Center for Health Statistics; 2009.
5. Marcus SF, Brinsden PR. Analysis of the incidence and risk factors associated with ectopic pregnancy following in-vitro fertilization and embryo transfer. *Hum Reprod*. 1995;10(1):199-203.
6. Tal J, Haddad S, Gordon N, Timor-Tritsch I. Heterotopic pregnancy after ovulation induction and assisted reproductive technologies: a literature review from 1971 to 1993. *Fertil Steril*. 1996;66(1):1-12.
7. Chin HY, Chen FP, Wang CJ, Shui LT, Liu YH, Soong YK. Heterotopic pregnancy after in vitro fertilization-embryo transfer. *Int J Gynaecol Obstet*. 2004;86(3):411-416.
8. Reece EA, Petrie RH, Sirmans MF, Finster M, Todd WD. Combined intrauterine and extrauterine gestations: a review. *Am J Obstet Gynecol*. 1983;146(3):323-330.
9. Practice Committee of the American Society for Reproductive Medicine; Practice Committee of the Society for Assisted Reproductive Technology. Guidelines on number of embryos transferred. *Fertil Steril*. 2009;92(5):1518-1519.
10. Practice Committee of Society for Assisted Reproductive Technology; Practice Committee of American Society for Reproductive Medicine. Guidelines on number of embryos transferred. *Fertil Steril*. 2008;90(5 suppl):S163-S164.

- 11.** Vitthala S, Gelbaya TA, Brison DR, Fitzgerald CT, Nardo LG. The risk of monozygotic twins after assisted reproductive technology: a systematic review and meta-analysis. *Hum Reprod Update*. 2009;15(1):45-55.
- 12.** Hershlag A, Paine T, Cooper GW, Scholl GM, Rawlinson K, Kvapil G. Monozygotic twinning associated with mechanical assisted hatching. *Fertil Steril*. 1999;71(1):144-146.
- 13.** Verpoest W, Van Landuyt L, Desmyttere S, Cremers A, Devroey P, Liebaers I. The incidence of monozygotic twinning following PGD is not increased. *Hum Reprod*. 2009;24(11):2945-2950.
- 14.** Chang HJ, Lee JR, Jee BC, Suh CS, Kim SH. Impact of blastocyst transfer on offspring sex ratio and the monozygotic twinning rate: a systematic review and meta-analysis. *Fertil Steril*. 2009;91(6):2381-2390.
- 15.** Silver RK, Helfand BT, Russell TL, Ragin A, Sholl JS, MacGregor SN. Multifetal reduction increases the risk of preterm delivery and fetal growth restriction in twins: a case-control study. *Fertil Steril*. 1997;67(1):30-33.
- 16.** Antsaklis AJ, Drakakis P, Vlazakis GP, Michalas S. Reduction of multifetal pregnancies to twins does not increase obstetric or perinatal risks. *Hum Reprod*. 1999;14(5):1338-1340.
- 17.** Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic sperm injection of a single spermatozoan into an oocyte. *Lancet*. 1992;340(8810):17-18.
- 18.** Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. *Endocr Rev*. 2009;30(5):465-493.
- 19.** Sauer MV. Extending reproductive potential in the older woman. In: Lobo RA, ed. *Treatment of the Postmenopausal Woman. Basic and Clinical Aspects*. New York: Raven Press; 1994:35-46.
- 20.** Practice Committee of Society for Assisted Reproductive Technology; Practice Committee of American Society for Reproductive Medicine. Preimplantation genetic testing: a Practice Committee opinion. *Fertil Steril*. 2008;90(5 suppl):S136-S143.

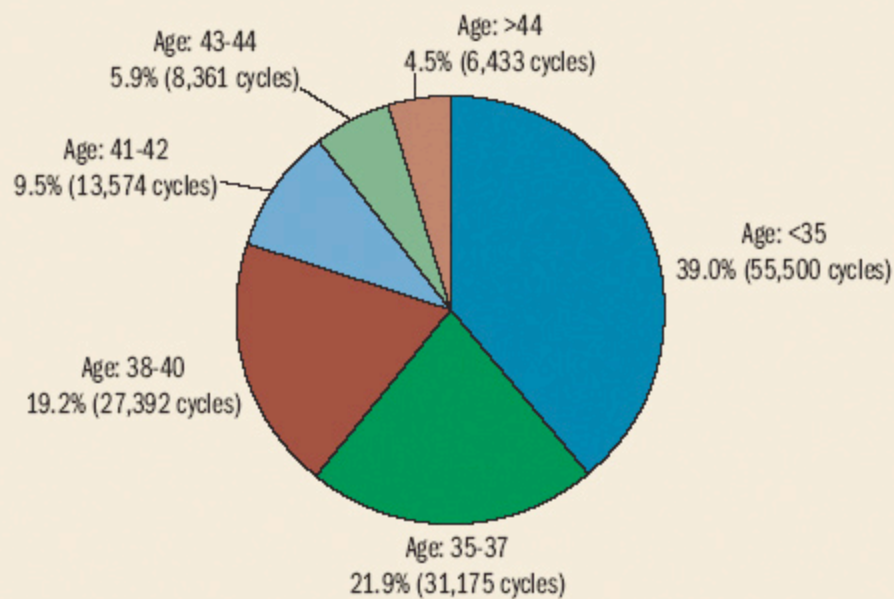
**FIGURE 1** Types of assisted reproductive technology by age group—United States, 2007



<sup>a</sup>Sum of percentages as shown within each bar does not equal the total shown at the top of each bar because of rounding.

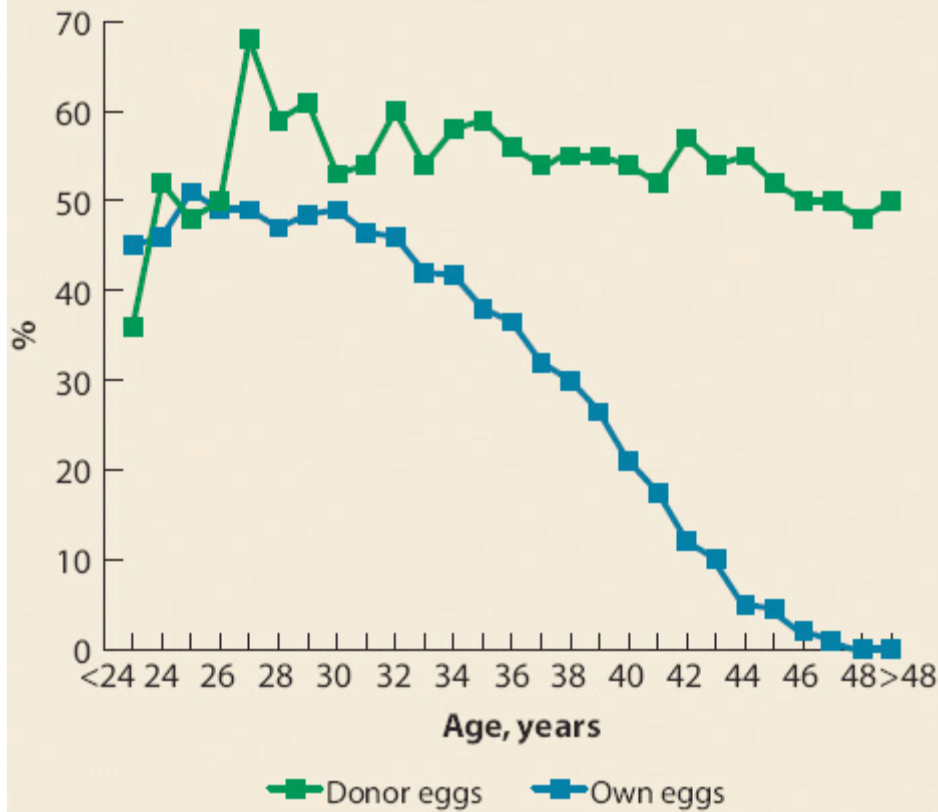
Adapted from Centers for Disease Control and Prevention.<sup>1</sup>

**FIGURE 2** Assisted reproductive technology by age group—United States, 2007



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