Single-Embryo Transfer Catches on in Europe

While SET becomes the standard of care in many countries, it's used much less often in the United States.

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COPENHAGEN — While single-embryo transfer rates for in vitro fertilization procedures languish below 2% in the United States, the Europeans are hitting astonishing highs with impressive results.

Aimed at reducing the growing multiple-pregnancy rate—which was once accepted as an unavoidable side effect of in-vitro fertilization (IVF)—single-embryo transfer (SET) has been enthusiastically embraced across much of Europe, particularly in the Nordic countries and Belgium. Indeed, SET made up 70% of Swedish embryo transfers last year, said Anders Nyboe Andersen, M.D., at the annual meeting of the European Society of Human Reproduction and Embryology.

The latest European figures (2002) show that of all clinical pregnancies achieved using assisted reproductive technology (ART), the rate of triplet pregnancies per transfer was just over 1%, and the rate of twin pregnancies per transfer was 23.6%, he said.

According to a 2002 report from the Centers for Disease Control and Prevention, the risk of having a pregnancy involving triplets or more per ART cycle was almost 7%, and the risk of a twin pregnancy was 29%. Dr. Andersen, head of the fertility clinic at the Rigshospitalet at Copenhagen University Hospital, noted that because of reporting differences, the U.S. and European data were not directly comparable.

Many fertility experts initially regarded SET as a necessary compromise: The possibility of multiple pregnancies was decreased at the price of a decrease in pregnancy rates overall. Indeed, supporters of this theory have pointed out that the failure of the United States to adopt the widespread use of SET has worked to the advantage of the overall rate of clinical pregnancies per ART cycle in the United States, which is 34.3%, about 5% higher than the European rate.

But the recent Swedish experience has vindicated SET in this regard, reported Karin Erb, laboratory director, fertility clinic, Odense (Denmark) University Hospital.

In a review of fertility data from the Nordic countries, which she presented at the meeting, Ms. Erb reported that stricter Swedish embryo transfer legislation introduced in 2003 forced a sharp increase in SET in that country, with no decrease in the country's overall IVF success rates.

Preliminary 2004 data for Sweden is "even more exciting," said Professor Karl Nygren of the department of obstetrics and gynecology at Sofiahemmet Hospital in Stockholm.

"The pregnancy rate per embryo transfer remained constant at around 30%, while the number of twin births plummeted to just 5%, and there were no triplet deliveries at all," he said in a written statement.

While SET becomes the standard of care in many European countries, fertility experts in the United States continue to regard it as a rarity.

"This is amazing. I didn't even know they were doing this," Jeffrey M. Jones, Ph.D., director of the andrology and IVF laboratory at the University of Wisconsin Medical School in Madison, commented in an interview after hearing some of the presentations at the meeting.

In 2002, SET made up just 1.2% of all IVF and intracytoplasmic sperm injection cycles in the United States, up from 0.8% in 2001. In 2004, for the first time, guidelines released by the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology recommended that SET be considered "for patients with the most favorable prognosis" (Fertil. Steril. 2004;82:773-4). The effect of those guidelines, however, will not be seen before the release of the 2005 data.

Certainly, not all centers can adopt SET without seeing at least an initial decrease in pregnancy rates—and patient selection is a key factor in this equation.

The world's first randomized trial comparing SET to double-embryo transfer (DET) in unselected patients is a case in point.

At the meeting, Aafke van Montfoort, M.D., of the Academic Hospital Maastricht (the Netherlands) reported data on 308 patients under age 41 who were randomized to SET or DET for their first IVF cycle. There were no twins in the SET group, compared with a twin rate of 21% in the DET group. The ongoing pregnancy rate was considerably lower after SET, however, at 21% vs. 40%, said Dr. van Montfoort.

But in another study presented at the meeting, patients were selected (aged less than 37, two top-quality embryos, and less than 20% embryo fragmentation), and given the choice of either SET or DET. The SET group had an ongoing clinical pregnancy rate of 39%, compared with 36% in the DET group, reported H.E. Bredkjaer, M.D., of Holbaek (Denmark) Sygehus Fertility Clinic.

According to many experts, it is important to judge SET beyond the context of the first fresh IVF cycle, because the approach often yields many frozen embryos, which can boost a patient's overall chances for pregnancy.

In Dr. van Montfoort's study of unselected patients, significantly more SET patients (52%) had excess embryos available for cryopreservation, compared with the DET patients (40%). However, even after all patients with frozen embryos underwent one subsequent frozen embryo cycle, the ongoing pregnancy rate remained considerably lower (29%) for the SET group, compared with the DET group (42%).

In Dr. Bredkjaer's study of selected patients, 93% of the SET patients had extra embryos cryopreserved, and 35% of these patients became pregnant on a subsequent frozen-embryo transfer.

Despite the promising data, Dr. Jones doesn't expect the European wave of enthusiasm for SET to catch on soon in the United States, and the main reason is financial.

"I don't think it's ever going to happen until it is mandated or there's insurance coverage for fertility treatment in the U.S.," he said in an interview. "In the Nordic countries there is insurance for IVF, and so patients are willing to undergo several cycles with single-embryo transfer. In the U.S., it's all out of pocket, so they want to get pregnant on the first attempt."

David K. Gardner, D.Phil., and associates at the Colorado Center for Reproductive Medicine published a study last year showing that with single-blastocyst transfer on day 5 (most European programs do single-embryo transfer on day 3), high ongoing pregnancy rates can be achieved on the first attempt (Fertil. Steril. 2004;81:551-5).

In Sweden, which has seen a sharp increase in SET, the pregnancy rate per embryo transfer is 30% and the twin birth rate was just 5% in 2004.

The prospective trial randomized 48 women to either single-blastocyst transfer or double-blastocyst transfer, and investigators found a comparable ongoing pregnancy rate of 61% and 76%, respectively, with a twin rate of zero in the single-blastocyst transfer group and 47% in the double-blastocyst transfer group.

"If SET can be performed with a high degree of success in appropriate patient populations, as is suggested by the current investigation, there are no financial or medical reasons not to recommend this approach," wrote the Colorado investigators.

Patients were eligible for the study if they met the center's criteria for blastocyst transfer: a day 3 FSH level of 10 mIU/mL or less, an estradiol level of less than 80 pg/mL, a hysteroscopically normal endometrial cavity, and at least 10 follicles measuring at least 12 mm on the day of HCG administration.

The authors acknowledged their difficulty in getting patients to volunteer for SET. "This was undoubtedly due to the perception by patients that SET could result in lower pregnancy rates and that twin pregnancies are a desirable outcome," they wrote.

Patient attitudes are undoubtedly a barrier to SET, but physicians' attitudes also can have a huge influence, said Christina Bergh, M.D., professor of obstetrics and gynecology at Sahlgrenska University Hospital in Goteborg, Sweden. A study she presented at the meeting found that physicians' attitudes toward SET in the various Nordic countries correlated strongly with the rates of SET and multiple births in those countries. "When aiming for a reduction in multiple births by introducing SET, IVF doctors are important targets," Dr. Bergh said.

"Most patients rely on doctors for advice," she said later in an interview. "My experience is they trust us; we are the experts." Convincing Swedish patients to try SET was much easier than had been expected, she said.

If U.S. physicians face a tougher time convincing their patients to choose SET, some new evidence could boost their powers of persuasion. SET may actually lead to lower miscarriage rates and better neonatal outcomes, compared with singleton pregnancies resulting from the transfer of more than one embryo. It has long been recognized that singletons conceived through IVF have a much poorer outcome than spontaneously conceived singletons.

Now some researchers report that this disparity could possibly be due to the effects of multiple-embryo transfer. Just as a vanishing twin has been shown to increase complications for the surviving fetus, recent evidence suggests that the demise of at least one embryo after a multiple-embryo transfer may create a toxic environment for the implanted surviving embryo.

A study presented at the meeting by Diane De Neubourg, M.D., supports this argument. After prospectively collecting obstetrical and neonatal data on 251 IVF singletons conceived after SET and more than 53,000 singletons that were spontaneously conceived, she found both groups had comparable outcomes.

Although a higher percentage of SET babies than spontaneously conceived babies (9.2% vs. 5.4%) was born prematurely (32-37 weeks), the mean birth weights and mean gestational ages of the groups were similar.

This compares with other studies showing increased perinatal mortality, increased birth rates of small-for-gestational age infants, and increased preterm delivery and low and very low birth weight in IVF singletons (most of whom are conceived after multiple-embryo transfer), said Dr. De Neubourg, a gynecologist at the center for reproductive medicine at Middelheim Hospital in Antwerp, Belgium.

In a recent editorial on SET, Owen K. Davis, M.D., immediate past president of the Society for Assisted Reproductive Technology, noted that "in 2001, women less than 35 years of age underwent approximately 47% of the IVF cycles in the United States, and 75% of the cycles were first or second attempts. Although the proportion with 'good quality' embryos is not known, this would suggest that on the order of 30% of cycles could be considered for single-embryo transfer" (N. Engl. J. Med. 2004;351:2440-2).

Assuming acceptance of SET by U.S. physicians, he continued: "The education of patients regarding the risk of twin as well as higher-order multiple pregnancy, along with improved insurance coverage for assisted reproductive therapies, would probably enhance the acceptance of a single-embryo transfer approach for appropriate candidates." ■