

fection, as compared with reexposure, also merits consideration. The authors conclude that the case here “is most consistent with reactivation of histoplasmosis, although a recent primary infection cannot be ruled out.” The reactivation hypothesis is less likely in this case, since the patient resided in a highly endemic area and had received systemic TNF- α blockers for the 4 years preceding the gene-therapy trial. In addition, calcified lesions have not been shown to contain viable organisms when cultured or after inoculation into experimental animals.²

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Cumulative Live-Birth Rates in a Trial of Single-Embryo or Double-Embryo Transfer

TO THE EDITOR: We previously reported in the *Journal*¹ the results of a randomized, controlled trial comparing pregnancy outcomes in patients undergoing in vitro fertilization (IVF) involving a fresh single-embryo transfer followed, if no live birth occurred after the fresh-embryo cycle, by a frozen-thawed single-embryo transfer with patients undergoing IVF involving a fresh double-embryo transfer. As compared with the rates in the double-embryo-transfer group, in the single-embryo-transfer group, the live-birth rate was not substantially lower and the multiple-birth rate was significantly lower.¹ Multiple birth is considered to be the main risk associated with IVF because of the increased rate of adverse perinatal outcomes.^{2,3}

The present study investigated the cumulative live-birth rates in the two groups after the inclusion of all frozen-thawed cycles after the fresh-embryo cycle. The cumulative live-birth rate was defined as the number of women with a pregnancy resulting in at least one live birth divided by the number of women who underwent randomization. In the additional frozen-thawed cycles, one or two embryos were transferred, without regard to the original randomization group. All 661 patients who participated in the randomized trial were included; none of the patients were lost to follow-up, and all embryos were accounted for (Fig. 1).

The cumulative live-birth rates were 43.9% (145 of 330 patients) in the single-embryo-transfer group and 51.1% (169 of 331 patients) in the

double-embryo-transfer group (difference, 7.1%; 95% confidence interval [CI], -0.6 to 14.8; $P=0.08$). The mean rate of live births was 53% (174 of 330 patients) in the single-embryo-transfer group and 57% (189 of 331 patients) in the double-embryo-transfer group ($P=0.20$). The multiple-birth rate was significantly lower in the single-embryo-transfer group than in the double-embryo-transfer group (2.3% vs. 27.5%; difference, 25.2%; 95% CI, 15.1 to 35.0; $P<0.001$). The rate of preterm birth (<37 full weeks of gestational age) was significantly higher in the double-embryo-transfer group as compared with the single-embryo-transfer group (25.5% vs. 11.8%; difference, 13.7%; 95% CI, 4.0 to 23.2; $P<0.001$) (see Table 1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

The use of cumulative live-birth rates instead of outcome per cycle has advantages for the patient, since it better summarizes her chance of a live birth over an entire treatment period.⁴ We found that the cumulative live-birth rate after one oocyte retrieval was high in both groups. It was lower in the single-embryo-transfer group than in the double-embryo-transfer group, although not significantly so. The advantage of single-embryo transfer is the dramatically reduced rate of multiple births as compared with double-embryo transfer. A well-functioning cryopreservation program is a prerequisite to implementation of a single-embryo-transfer strategy and should be encouraged.⁵

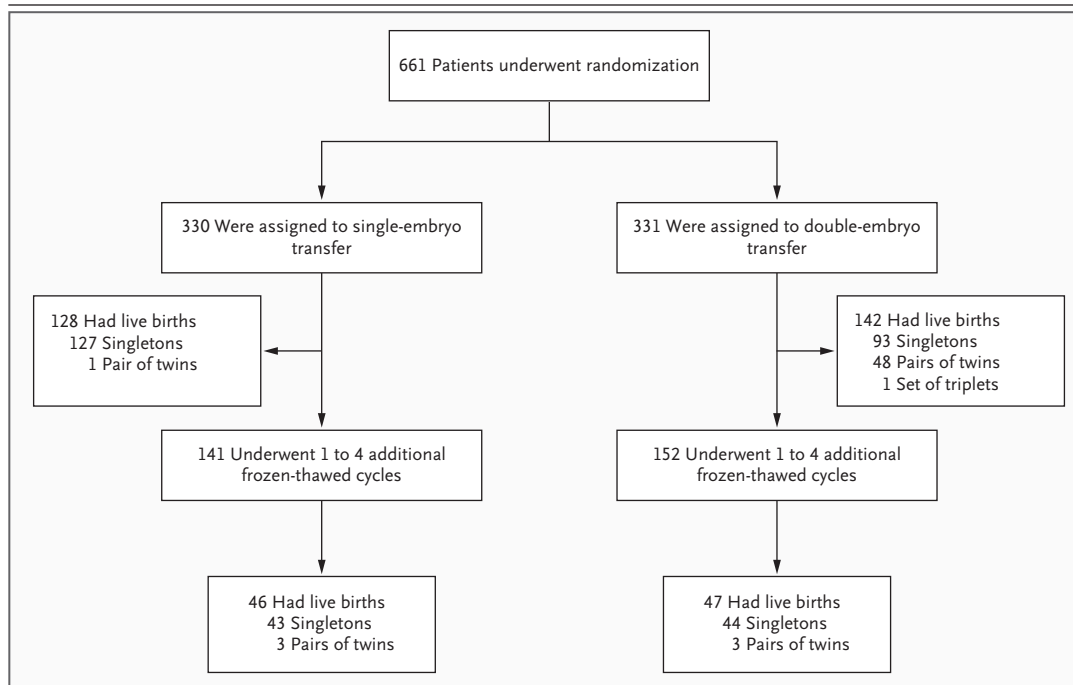


Figure 1. Enrollment and Outcomes.

The patients in the single-embryo-transfer group underwent one fresh single-embryo transfer, and if no live birth occurred after one cycle, these patients underwent one frozen-thawed single-embryo transfer. Patients in the double-embryo-transfer group underwent one fresh double-embryo transfer. Twenty-nine patients in the single-embryo-transfer group and 18 patients in the double-embryo-transfer group had pregnancies resulting in two live births. One woman in the double-embryo-transfer group had a pregnancy resulting in three live births. The 48 pairs of twins in the double-embryo-transfer group after the first cycle included three twin pregnancies in which one fetus died in utero between 24 and 27 weeks of gestational age.

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Supported by Sahlgrenska Academy, Sahlgrenska University Hospital, and the Göteborg Medical Society.

Dr. Thurin-Kjellberg reports receiving lecture fees from Merck Serono, Schering-Plough, and Ferring, and consulting fees from Merck Serono Sweden; and Dr. Bergh, lecture fees from Merck Serono, Schering-Plough, and Ferring. No other potential conflict of interest relevant to this letter was reported.

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