Article

# Elective single embryo transfer versus double embryo transfer in assisted reproduction

Dr Moustafa graduated from Al-Azhar University, and is an assistant professor at the Department of Obstetrics & Gynecology, Azhar University. He is currently working as an IVF consultant at Erfan Hospital, Jedda.

*Dr Mohamed Khaled Moustafa*

Mohamed Khaled Moustafa[1,4], Sheded Ashour Sheded[1,2,3], Mohamed Abd El Aziz Mousta[1]
[1]Dr Erfan and Bagedo General Hospital, Jeddah, Saudi Arabia; [2]Al Azhar University, Cairo, Egypt; [3]Cairo University, Cairo, Egypt
[4]Correspondence: drkhaledivf@yahoo.com

## Abstract

High numbers of embryos transferred during assisted reproduction have become implicated as the cause of higher than normal twinning and multiple gestation rates following this form of therapy. However, reducing the number to a single embryo transferred has been shown to carry unfavourable results in the first cycle, but with similar cumulative live birth rates. This study tested the theory by performing a randomized controlled trial of elective single embryo transfer (SET) versus double embryo transfer (DET) in young women, and follow them up for 1 year to determine the result of cryo-embryo transfer cycles in the two cohorts. The results showed that the probability of a live birth was not significantly different between the two groups, but with a higher rate of twins in the DET group. In addition, during the 1-year follow-up period, the live birth, clinical pregnancy and multiple pregnancy rates were also similar, and in line with the results of the randomized trial. In conclusion, the results of this prospective randomized trial and 1-year follow-up show that in young women, elective SET should be the first line of choice. Even so, these results should be confirmed by larger randomized studies.

***Keywords:*** *cryo-embryo transfer, follow-up, live birth rates, pregnancy rates, randomized controlled trial, single embryo transfer*

## Introduction

Assisted reproduction technologies have become socially accepted as treatment options for infertile couples seeking to have a child. These options, coupled with the marked improvements in ovarian stimulation protocols, techniques for sperm retrieval, laboratory techniques and techniques for embryo transfer, have sharply increased the hopes of having a child for infertile couples. At the same time, the improved pregnancy rates have carried the burden of a higher than normal chance of a multiple gestation. This has resulted in calls for milder ovarian stimulation protocols and the transfer of fewer embryos, in order to offset this increased risk rate of multiple and higher order gestations (Van Voorhis, 2006).

In contrast to the once-believed theory, the numbers of embryos transferred and the incidence of a clinical pregnancy are not proportionally related. It was shown that in women the policy of double embryo transfer (DET) was as effective as multiple single embryo transfer, but at the same time carried a greater risk of multiple gestations than the latter policy (Templeton and Morris, 1998; Veleva *et al*., 2006). This policy has effectively diminished the triplet and quadruplet pregnancy rates following IVF in many countries. Even so, a significant rate of twin pregnancies following IVF is still common.

In addition, twin pregnancies are at a higher risk of preterm labour than singleton pregnancies (Verstraelen *et al*., 2005). Preterm birth is a major cause of serious health problems in neonates, including respiratory distress, difficulty regulating body temperature and infection. More than 85% of long-term disabilities in otherwise healthy babies and 75% of deaths among newborns occur as a result of preterm delivery (Sutcliffe and Derom, 2006).

During recent years, there have been efforts to reduce the incidence of twin pregnancies by transferring fewer embryos.

Many European countries, encouraged by the success in decreasing the twin pregnancy rates in Scandinavian countries, have developed extensive plans, legislation and recommendations to patients and infertility clinics to institute more conservative transfer practices (Ombelet *et al.*, 2005).

To resolve the issue of twin pregnancies following IVF further, an elective single embryo transfer (SET) policy has been proposed. Randomized controlled trials comparing elective SET and DET have shown relatively similar results between the two policies, but with fewer twin pregnancies with elective SET (Vauthier-Brouzes *et al.*, 1994; Gerris *et al.*, 1999; Mantikainen *et al.*, 2001; Lukassen *et al.*, 2002). Even so, a recent Cochrane systematic review concluded that the clinical pregnancy rate following elective SET was significantly less than that for DET (Pandian *et al.*, 2004). This may reflect a lack of statistical power in the individual studies to detect a difference.

To offset this possible difference in the pregnancy rates between the two groups, it has been proposed that the addition of one cycle of elective SET plus one cycle of single cryo-embryo transfer will equalize the difference in pregnancy rates, but at the same time decrease the twin pregnancy rates (Thurin *et al.*, 2004). Therefore, a randomized controlled trial of elective SET versus DET in young women was performed, with follow-up for 1 year to determine the result of cryo-embryo transfer cycles in the two cohorts.

# Materials and methods

This prospective, randomized trial was approved by the institutional review board. Eighty-one patients undergoing embryo transfer in the assisted reproduction unit (Dr Erfan Hospital) between September 2004 and September 2006 were prospectively included.

## Patient population

The study objectives were explained thoroughly to all prospective patients and their partners entering the assisted reproduction programme. Couples who agreed to enter the clinical trial provided both verbal and written consent. Inclusion criteria were: (i) women undergoing embryo transfer in a fresh cycle; (ii) at least one good quality embryo (Grade I–II) on the day of transfer; (iii) women's age ≤30 years at the time of embryo transfer; and (iv) no contraindication for pregnancy. Exclusion criteria were: (i) women's age >30 years; (ii) only poor quality embryos available for transfer; and (iii) refusal to consent or participate in the clinical trial. Patients were randomized on the day of transfer to one of the two groups. Randomization was performed by a third party (a nurse) who was not involved in any other aspect of the study.

In addition, patients were followed up for 1 year to determine the results of cryo-embryo transfers. The number of embryos transferred during this period was the same as the original randomization.

## Ovulation induction and IVF protocols

All aspects of the IVF procedure including medication and fertilization protocol were similar between the two groups, with the exception of the number of embryos transferred. In brief, ovarian stimulation, oocyte retrieval and luteal phase support were performed in accordance with the standard protocol of the department. Women were down-regulated using a gonadotrophin-releasing hormone (GnRH) agonist (Decapeptyl; Ferring NV, Belgium) protocol, followed by ovarian stimulation using recombinant FSH (rFSH, Puregon; NV Organon, Oss, The Netherlands) and/ or human menopausal gonadotrophin (Menogon; Ferring NV) until the day of human chorionic gonadotrophin (HCG) administration. When the leading follicle reached ~18 mm in diameter, 10,000 IU of HCG (Pergnyl; NV Organon,) was given intramuscularly, and oocyte retrieval was performed 34–36 h later. Intracytoplasmic sperm injection was performed for all cases as standard and injected oocytes were cultured using VitroLife culture media (VitroLife, Sweden). Embryo quality was assessed by two embryologists (Baxter Bendus *et al.*, 2006) and surplus embryos were frozen and thawed according to the standard method (Kattera *et al.*, 1999). Luteal phase support was provided in the form of daily progesterone vaginal suppositories three times daily (Cyclogest 400 mg; Hoechst Roussel Limited, UK).

## Embryo transfer technique

All embryo transfers were performed on day 2–3 by the same physician using a standardized technique. Embryo transfer was performed using a Wallace embryo replacement catheter connected to a tuberculin syringe. In both groups, the aim was to deposit the embryos ~2 cm from the uterine fundus under ultrasound guidance with a full bladder.

## Outcome measures

The primary outcome measures for this trial were the live birth and multiple pregnancy rates per randomized woman. Live birth was defined as a living fetus born ≥28 weeks of gestation. In addition, the clinical pregnancy rate, multiple pregnancy rate, gestational age at miscarriage, gestational age at birth and fetal weight at birth in the two groups were investigated. Clinical pregnancy was defined as increasing maternal serum β-HCG concentration combined with an intrauterine gestational sac and positive fetal heartbeat visualised on ultrasound examination.

## Statistical analysis

Statistical analysis was performed according to the intention to treat principle. All analyses of significance were two-sided and tested at the 5% level; values of $P < 0.05$ were considered to indicate significant differences. Continuous variables were tested if they presented normal distribution using the *F*-test. The results of the two groups were compared using Student's *t*-test or the Mann–Whitney *U*-test for parametric and non-parametric data, respectively. Qualitative variables were compared using the chi-squared test with Yates correction or Fisher's exact test, when necessary, and the 95% confidence intervals (CI) using the Woolf (logit) approximation. Odds ratios (OR) and 95% CI were calculated to examine the odds of improving clinical outcomes. Clinical and demographic data are also presented as mean (± SD) or as frequency distribution for simplicity. Statistical analysis was performed using the computer statistical package Stats Direct (Stats Direct Ltd, UK).