Reducing twin pregnancy rates after IVF elective single embryo transfer (eSET)

P Milne, E Cottell, C Allen, H Selhane, J Vassalo, M Wingfield
Merrion Fertility Clinic, National Maternity Hospital, Holles Street, Dublin 2

Abstract
Multiple pregnancy is a major complication of IVF and is associated with increased maternal, fetal and neonatal morbidity. Elective single embryo transfer (eSET) during IVF, rather than the more standard transfer of two embryos (double embryo transfer or DET), has been shown to significantly reduce the multiple pregnancy rate associated with IVF, while maintaining acceptable pregnancy rates. Couples undergoing IVF in 2008 who met good prognostic criteria had eSET performed. Pregnancy and twinning rates were compared with those for similar couples in 2007 who had DET. Couples unsuccessful with a fresh cycle of treatment had subsequent frozen embryo transfer cycles with DET. The cumulative pregnancy rate was similar for each group. However there were no multiple pregnancies in the eSET group, compared to 4 twin(s) in pregnancies in the DET group. 96% of eligible couples agreed to eSET. ESET is successful in and acceptable to good prognosis Irish couples undergoing IVF.

Introduction
Assisted conception births account for more than 1% of all births in the UK and Europe. Multiple pregnancies contribute the vast majority of morbidity associated with in-vitro fertilisation (IVF). They involve more complications for mothers and babies, with clear increases in caesarean section, prematurity, low birth weight, and infant disability and death. Standard IVF practice currently involves the transfer of 2 embryos to the uterine cavity, with up to 3 embryos transferred when the prognosis is less favourable. While this approach has significantly reduced the incidence of triplet and higher order multiple pregnancies, the incidence of twin pregnancies remains unacceptable. The incidence of triplet (intracytoplasmic sperm injection) treatment at Merrion Fertility Clinic (MFC) who were perceived to have a good prognosis were offered the option of eSET rather than DET. The six of these 274 couples (9.8%) that consented to eSET in 2008 was compared with those for ‘good prognosis’ couples who had DET in 2007. Outcomes for the “eSET-eligible” couples for 2007 and 2008 were compared

Methods
Between 1st January and 31st December 2008, 69 couples undergoing IVF or ICSI (intracytoplasmic sperm injection) treatment at Merrion Fertility Clinic (MFC) who were considered to have a good prognosis, were offered the option of eSET rather than DET. The criteria for ‘good prognosis’ were (i) female age less than 36 years, (ii) first cycle of IVF/ICSI treatment and, (iii) one superior quality embryo and two others suitable to transfer on the day of embryo transfer. Embryos were graded as superior quality if they had 4 or 5 cells with <10% fragmentation (grade 1 or grade 2a) on day two and as suitable to transfer if they had 2, 3, 4 or 5 cells and were graded 1, 2a or 2b based on previously published criteria. Couples were excluded if previous IVF/ICSI treatment had been cancelled prior to oocyte retrieval due to poor response to stimulation; those previously cancelled due to ovarian hyperstimulation were included. Couples were included if they had a previous history of single pregnancy following a fresh cycle. Couples requesting eSET, regardless of embryo quality and couples having eSET for medical reasons were excluded. If pregnancy did not follow the first fresh eSET, a subsequent frozen embryo transfer cycle with double embryo (DET) was offered. Clinical pregnancy rates were calculated for the fresh eSET and for the frozen cycles. The cumulative pregnancy rate was calculated by combining the outcome for one fresh and any frozen transfer cycles using embryos frozen during the original fresh cycle. Data was reviewed for all couples treated in the previous year, 2007, who would have met the criteria for good prognosis as described above. In 2007 the policy was to perform DET in all cycles. The cumulative pregnancy and twinning rates for good prognosis couples having eSET in 2008 was compared with those for good prognosis couples who had DET in 2007. Outcomes for the eSET-eligible couples for 2007 and 2008 were compared using the Wilcoxon-Mann Whitney two sample rank sum test.

Results
In 2008, 274 fresh embryo transfers were performed at MFC. Of these, 69 (25.2%) were in women under 36 years, undergoing their first complete cycle of IVF or ICSI treatment. Forty nine out of these 69 fulfilled the eligibility criteria for eSET at the start of the treatment cycle. All were counselled regarding the risks of multiple pregnancy and the clinic’s eSET policy. Forty eight of the 49 couples (98%) consented to eSET, should they have suitable embryos at transfer. On day 2 following oocyte retrieval, 21 of the 48 couples (44%) had good prognosis embryos fulfilling the criteria for eSET. One of these 49 couples had previously failed multiple attempts with IVF. The remaining 20 couples had eSET performed. This was done on day 2 for all except one couple who had a day 3 transfer because of abdominal pain following oocyte retrieval.

Nine women (45%) conceived and 8 (40%) had a viable singleton clinical pregnancy as evidenced by a fetal heart seen at a seven week scan. To date three of these women have delivered healthy singleton babies and the remaining five are currently well with continuing pregnancies greater than 17 weeks (17, 17, 17, 25, 34, 36). Of the 12 women in this eSET group who were unsuccessful on their fresh cycle (11 not pregnant, one biochemical pregnancy), 10 have subsequently had a frozen embryo transfer cycle with DET. Of these, 8 conceived (64%) and all have viable singleton pregnancies. To date, one has delivered a healthy singleton and the remaining four are all more than 35 weeks gestation. Two couples have not yet had a frozen embryo transfer cycle following their failed fresh cycle. The cumulative clinical pregnancy rate for this group i.e. clinical pregnancy rate following one fresh and one frozen cycle embryo transfer is 72% (13/18). Of the seven who have not yet conceived, 6 still have additional embryos frozen (mean no = 4) so may yet conceive as a result of their initial IVF/ICSI cycle.

In 2007, 234 embryo transfers were performed at MFC. Of these, 53 were in women aged 35 years or less, undergoing their first cycle of IVF or ICSI treatment. Only 9 of these had embryos of sufficient quality to fit the 2008 good prognosis eSET criteria. In line with clinic policy at the time, all had DET performed. Six of the eight women conceived, 1 with a biochemical and 5 with viable clinical pregnancies (clinical pregnancy rate 62.5%). Four of the five clinical pregnancies were twin (88%). Of these, one woman lost a twin at nine weeks and went on to deliver a healthy singleton at 42 weeks. Two women delivered healthy twins at 35 and 36 weeks gestation. The fifth woman tragically delivered both twins at 19 weeks gestation. Of the 5 women who did not conceive on their fresh cycle (2 not pregnant, one biochemical pregnancy) all three have subsequently had a frozen embryo transfer cycle with transfer of two embryos. None of these frozen cycles was successful. The cumulative clinical pregnancy rate for this group following one fresh and one frozen cycle embryo transfer is 52.5% (5/9). Of the 3 who have not yet conceived, one couple still has one remaining embryo frozen so may yet conceive as a result of their initial IVF/ICSI cycle.

Discussion
Concerns persist regarding the safety of IVF because of the potential health impact on mothers and infants. Twin pregnancies are a major complication of IVF, but remain a frequent outcome. Compared to singleton transfers, twin pregnancies are associated with a five-fold increase in stillbirth, a seven-fold increase in neonatal mortality, and a five-fold increase in infant mortality. While the mean gestational age at delivery is 35 weeks for being compared to 38 for singletons, and the incidence of low birth weight (<2500g) is 56.6% and 6.3% respectively. Prematurity is associated with intraventricular haemorrhage, necrotising enterocolitis and respiratory distress syndrome, and the incidence of cerebral palsy is increased five to ten fold. Maternal morbidity and mortality in early pregnancy is increased three-fold with associated higher risks of obstetric haemorrhage, diabetes and hypertension. All risks are higher again for triplet and higher order pregnancies.

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Effective single embryo transfer provides clear potential for reducing multiple pregnancy rates. Pioneered in Scandinavia, particularly Finland and Sweden, eSET was subsequently implemented in other European countries such as Belgium and the Netherlands. By employing an eSET policy, many clinics in Finland have reduced their twin pregnancy rate to less than 10%.11,13,14 Our study demonstrates for the first time that eSET is feasible, and indeed to be recommended, for good prognosis couples attending an Irish fertility clinic. ESET is acceptable to the majority of eligible couples in our clinic. While the numbers of twin pregnancies in this study are small, the outcome in terms of fetal loss is high. The tragedy of losing normally formed twins at 19-20 weeks gestation, as in one of our cases, exemplifies this.

It is imperative that all couples are offered treatments with optimal chances of success. Critics of eSET emphasise the reduced success rates in the initial fresh cycle compared with DET. Our figures reflect this; fresh cycle clinical pregnancy rates were 40% with eSET vs 62.5% with DET. However this increased success rate for DET is only achieved via an unacceptable incidence of twin pregnancy (4 out of 5 pregnancies in our study). By performing eSET for the first cycle, but by also freezing the remaining embryos for subsequent frozen embryo transfer, the cumulative pregnancy rate equals that of DET (72.2% for eSET and 62.5% for DET). While this protocol may pose a delay in the time-to-conception for up to 50% of eSET couples, the resulting pregnancy is highly likely to be a singleton.

Critics also maintain that an eSET policy may be more costly for couples if it involves both a fresh and a frozen cycle, rather than just one fresh cycle with DET. However financial considerations should not be the dictator of clinical practice. Indeed it has been shown in Belgium that reducing the twin pregnancy rate associated with assisted reproduction by 30% and that of triplets and higher order multiples to almost zero, results in such savings in neonatal intensive care costs that the laboratory costs for 7000 cycles of IVF-ET per annum can be funded. Six cycles of treatment per couple are now fully funded in that country with strict criteria for eSET. These estimated savings from the eSET policy, did not take into account the additional national savings resulting from the birth of an estimated 38 less children per annum with severe handicap.

In summary, critics of eSET argue that it is unacceptable to patients on the basis of (i) lower pregnancy rates in the fresh cycle, (ii) the need for subsequent frozen embryo transfer, and (iii) extra cost and time delay. This has not been the case in our study. Ninety six per cent of eligible couples in our group were willing to undergo eSET if they reached the embryologic inclusion criteria. The numbers in our study are small and not statistically significant, but echo the findings of others. They illustrate that for good prognosis couples as described here, eSET should be recommended.

Correspondence: C Allen
Merrion Fertility Clinic, National Maternity Hospital, Holles St, Dublin 2
Email: catherineallen@eircom.net

References