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# **Multiple Pregnancy Following Assisted Reproduction**

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## 1. Introduction

Multiple pregnancy is the most common adverse outcome of assisted reproduction technologies (ART) and reflects the standard practice of replacing multiple embryos in the uterus during in vitro fertilisation (IVF) treatment. Although iatrogenic multiple pregnancy is essentially preventable by the replacement of only a single embryo, the rate in the UK remains unacceptably high. The most recent UK-wide verified data from the Human Fertilisation & Embryology Authority (HFEA), covering the period between 1 January and 31 December 2007, showed a 0.3% increase to 23.0% in the percentage of multiple births arising from IVF and intracytoplasmic sperm injection in comparison with the previous year (Table 1). The 23.0% multiple birth rate is in stark contrast to the 6% multiple birth rate achieved in the same period in Sweden and Finland (countries with high state funding of IVF), even though overall IVF live birth rates are broadly comparable.

In response to concerns about the high numbers of twin and triplet pregnancies arising from ART, HFEA established a Single Embryo Transfer Expert Group, chaired by Professor P Braude, which reported in December 2006. The report, *One child at a time*,<sup>1</sup> identified the significant risks to the health of the offspring that result from twin and triplet gestation compared with singleton pregnancies. These risks are higher at all stages of pregnancy and include miscarriage, gestational diabetes and pre-eclampsia, impaired fetal growth and stillbirth, and problems during labour including intrapartum hypoxia and increased need for elective and emergency caesarean section.

Most significantly in terms of morbidity, mortality and cost, twin pregnancy carries a five- to six-fold increase in the risk of preterm birth. Preterm birth is often followed by a prolonged stay in neonatal intensive care. This leads in turn to an increased risk of long-term mental and physical handicap including cerebral palsy, mental disability, long-term learning difficulties and chronic lung disease. According to the Centers for Disease Control and Prevention, the number of twin births has doubled in the US since 1980, with over 23 000 IVF twins and a single-embryo transfer (SET) rate for women under 35 of only 4.5%.<sup>2,3</sup>

## 2. Why is the UK multiple pregnancy rate so high, and how can it be reduced?

Given these substantial increased risks, why does the rate of double-embryo transfer (DET) remain high? The answer lies in the nature of the relationship between IVF clinics, which strive to maintain a high position in the success rate 'league table', and desperate couples, whose desire to maximise the chance of pregnancy far outweighs the fear of adverse outcomes of a treatment they believe may be an apparently ideal outcome<sup>4</sup> and may allow them to achieve a family more quickly and cheaply if they

**Table 1.** Trends in multiple pregnancy rate from IVF, UK HFEA data 2005–2007

	2005	2006	2007	% change 2006–2007
<b>In vitro fertilisation (IVF)</b>				
Number of cycles of IVF	41 392	44 275	46 829	Up 5.8%
Number of patients undergoing IVF	32 626	34 855	26 861	Up 5.8%
Number of babies born through IVF	9058 successful births giving rise to 11 262 babies	10 242 successful births giving rise to 12 596 babies	11 091 successful births giving rise to 13 672 babies	Births up 8.3% Babies up 8.5%
IVF live birth rate per cycle started	21.6%	23.1%	23.7%	Up 0.6%
Multiple birth rate following IVF	24%	22.7%	23.0%	Up 0.3%

From HFEA fertility facts and figures September 2009 (see [www.hfea.gov.uk](http://www.hfea.gov.uk)). Data refer to all IVF/ICSI cycles using fresh or frozen embryos from the patient's own or donated eggs.

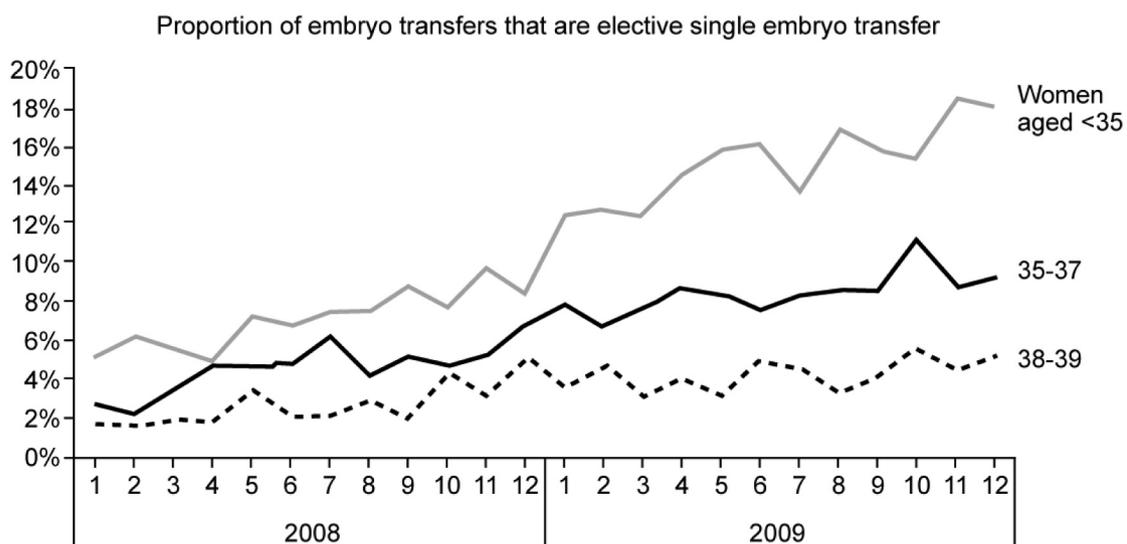
conceive a twin pregnancy. It remains the case that the pregnancy rate is higher following replacement of two embryos rather than one embryo, and this single fact is a powerful driver. Couples desperate to have a child may fail, either consciously or unconsciously, to consider fully the devastating consequences of having one or more children affected by cerebral palsy, neurodevelopmental delay or other serious long-term medical conditions. Internationally, there is a linear relationship between the amount of state funding for IVF and the rate of SET.<sup>5,6</sup> Those who have to pay often large sums from their own resources unsurprisingly seek to complete their family as cheaply as possible, whereas a policy of single fresh transfer with subsequent frozen embryo replacement (FER) is attractive in countries in which state reimbursement is the norm. Several studies clearly show that SET plus FER achieves an equivalent pregnancy rate to DET in young patients,<sup>7,8</sup> but this policy may result in a longer average time to pregnancy and, in the competitive UK market, a lower position in the IVF league table (which is based on live birth rate per cycle started). Recent moves towards transfer of a single embryo at blastocyst stage might improve success rates of SET and shorten time to pregnancy significantly.<sup>9</sup> The fact that the NHS rather than the privately funded fertility clinic is responsible for the subsequent pregnancy care of the woman (and her babies) reduces the clinic's incentive to limit the rate of multiple pregnancy.

A highly influential recent publication from Källén and colleagues<sup>10</sup> summarises the long-term picture of IVF and its complications in Sweden, one of the first countries to adopt a policy in favour of SET. The IVF twin rate peaked in Sweden at over 30% in 1992. An abrupt fall in IVF multiples since 2003 has resulted in a current twin rate of 5%, with an equivalent reduction in rates of preterm birth and low-birthweight infants. The majority of IVF cycles in Sweden are state funded, allowing easier implementation of a selective SET policy.

### 3. Progress towards increased single-embryo transfer

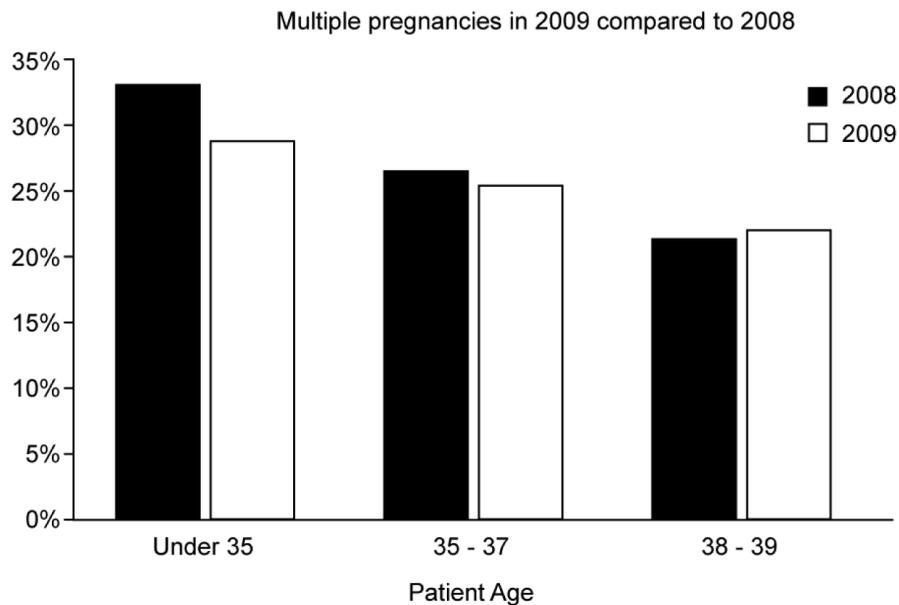
In the UK, the HFEA adopted a 'one at a time' policy after publication of its working party report, and has set a target for 2011 of no more than 20% multiple pregnancies for any clinic. This is based on identification by individual clinics/funding authorities of key patient groups at highest risk of multiple pregnancy from DET, to whom SET will be strongly recommended – a self-regulation model. Generally, these patients will include younger couples having a first IVF cycle. Some may regard this as liberal, given the upward trend already observed, but constraints on NHS funding mean that over 50% of IVF cycles in the UK are paid for by infertile couples themselves and the above-mentioned financial pressures therefore continue to apply. Sadly, a minority of those commissioners that do fund a significant amount

**Figure 1. Proportion of embryo transfers that are elective single-embryo transfer**



Data extracted from HEFA register 18 March 2010. 2009 data are unverified. Data refer to IVF/ICSI cycles from fresh embryos from the patient's own eggs only.

**Figure 2. Trends in IVF multiple pregnancy rate by age of woman, 2008–2009**



Data extracted from HFEA register 18 March 2010. 2009 data are unverified. Data refer to IVF/ICSI cycles from fresh embryos from the patient's own eggs only.

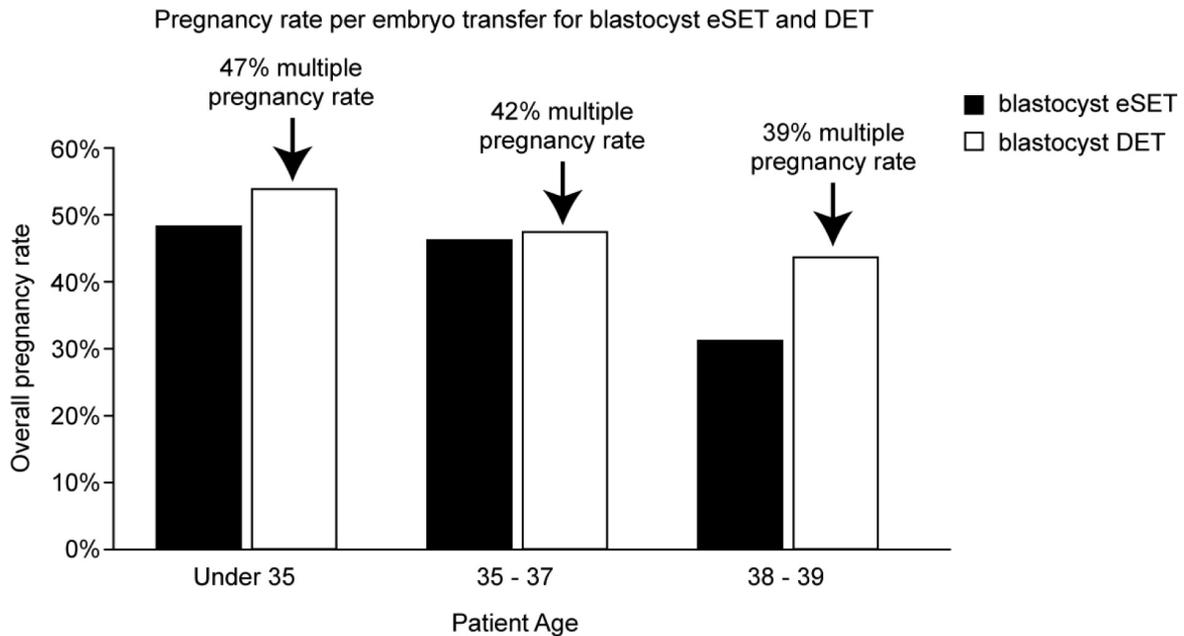
of IVF have misinterpreted the findings of the HFEA working party and others, and have enforced a mandatory SET policy on all patients who receive funded treatment. Overly rigid rules applied by commissioners merely drive couples into the private sector or overseas to obtain DET, defeating the object of the policy and possibly increasing rather than decreasing the multiple pregnancy rate, although there are examples of positive changes by, for example, including the use of frozen embryos in the funding of a cycle. Several countries, including Sweden, Belgium, Australia and New Zealand, have implemented a selective SET policy, relying on the clinician to determine who should still have two embryos replaced. Older patients and those who have had multiple failed cycles should be offered the opportunity to have DET in tightly defined circumstances.

The HFEA has promoted a voluntary, selective SET policy over the last 3 years. The most recent data (Figures 1 and 2) show a positive response from IVF clinics with a reduction in DET and a fall in the multiple pregnancy rate in younger women. Time will tell whether this 'light touch' approach is sufficient to achieve the desired multiple pregnancy rate in all clinics, which is still 20-fold higher than the normal twin rate, or whether specific regulation will be required. Additional reporting of data on the outcome of IVF multiple pregnancies would be valuable. Many clinics are moving to blastocyst transfer, particularly for younger patients. While more technically challenging for embryologists, and requiring investment in staff and equipment, blastocyst transfer allows more accurate grading of embryos with selection of the 'best' embryo for transfer, thus maintaining a good pregnancy rate using blastocyst SET.<sup>11</sup> This approach does, however, reduce the number of embryos frozen for later use, and data on the long-term safety of blastocyst transfer are limited. Twin rates for blastocyst DET are unacceptably high, even for older patients (Figure 3), and this practice should be discouraged. There is also continuing uncertainty regarding the long-term health effects of prolonged in vitro culture.<sup>12</sup>

#### 4. Opinion

The burden that iatrogenic, avoidable twin pregnancy places on couples, on their offspring and on society is too high. What should be done to influence practice and reduce the incidence of IVF twins to single figures?

**Figure 3. Multiple pregnancy rates for single- and double-blastocyst transfer after IVF**



Data extracted from HFEA register 18 March 2010. 2009 data are unverified. Data refer to IVF/ICSI cycles from fresh embryos from the patient's own eggs only.

First, the example of best practice set by some UK fertility clinics should be promoted as widely as possible to encourage practitioners who are not convinced that they can achieve high pregnancy rates with blastocyst SET for selected patients.

Second, commissioners should be discouraged by the Department of Health from trying to manage the details of specialist medicine. This is a problem in many areas of practice, but has clear negative influence in the field of infertility treatment. Commissioners should adhere to the 2004 National Institute for Health and Clinical Excellence (NICE) guidelines on management of the infertile couple, which set out a clear, simple and sensible policy for the provision of three full cycles that can be implemented if funding is provided.

Third, much is expected of the current review of the NICE guidelines, due for publication in early 2011. This review should include clear recommendations on the use of SET, evidence of the costs to the state of prolonged neonatal care and handicap from iatrogenic twins and higher-order multiple pregnancies, and recognise the link between provision of state support for IVF and acceptance of SET.

Fourth, organisations including the RCOG, British Fertility Society, HFEA and Department of Health should continue to develop a joined-up approach to promoting singleton birth as the norm for IVF patients in conjunction with patient groups,<sup>13</sup> emphasising the benefits to both mother and child and highlighting the risks of multiple pregnancy without overdramatisation.

As we enter a period of financial austerity, the benefits of SET to the NHS are unchallengeable. Large financial savings can follow from a reduction in the number of multiple pregnancies<sup>14</sup> and the concomitant pressure on neonatal and postnatal care. However, this can only follow from modest but focused NHS investment in funding IVF treatment to promote a rational SET policy.

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