

# IVF twins: buy one get one free?

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## Abstract

There has been an overall increase in the incidence of multiple pregnancies and assisted reproduction technology is largely responsible for this rise. Although twins may appeal to couples undergoing *in vitro* fertilisation (IVF), they have been associated with serious health consequences to the babies, their mothers and the family unit, as well as having massive financial implications for the National Health Service. Transfer of more than one embryo during IVF is mainly responsible for IVF twins, and elective transfer of a single embryo at a time with cryopreservation of surplus embryos for later transfer has been shown to be an effective strategy to minimise the risk of twins without compromising IVF success rates. Factors that will impact on the success of the policy of elective single embryo transfer (eSET) include improvement in embryo selection for transfer; better cryopreservation techniques and adequate state funding for IVF. However, in implementing the policy of eSET it is important that each case is assessed on an individual basis since in some situations (e.g. in older women) the transfer of two embryos may be more cost effective. Adequate and continuous education of all stakeholders is essential if the policy of eSET is to be successful in the UK.

## Introduction

Assisted reproduction techniques (ART) have substantially improved conception rates in couples with subfertility.<sup>1</sup> An increasing number of couples in the UK are accessing this treatment as evident by data from The Human Fertilisation and Embryology Authority (HFEA). In 2010, over 47 000 women underwent ART in the UK, an increase of 17% from 2008.<sup>1</sup> Of these, only 14.9% of treatment cycles were completed with the transfer of a single embryo.<sup>1</sup>

Surveys of subfertile couples have shown a popular desire for multiple pregnancies.<sup>2-4</sup> However, multiple pregnancies have been identified as one of the most significant risks of ART.<sup>3</sup> This complication of ART seems to be underestimated by the patients and even some clinicians.

This review article examines the rising problem of multiple pregnancies resulting from ART, outlines why patients and some clinicians may find twins appealing, and discusses measures to minimise the

## Key message points

- ▶ The overall increase in the incidence of multiple pregnancy is largely due to assisted reproduction technology.
- ▶ Twin pregnancies are associated with an increased perinatal morbidity and mortality to the babies and their mothers and also have financial implications for the National Health Service.
- ▶ Elective transfer of a single embryo in good prognosis patients reduces the incidence of twins without compromising *in vitro* fertilisation success rates.

incidence of this fundamental impediment to assisted conception.

## Why subfertile couples may prefer twins

The desire for twin pregnancies among couples seeking fertility treatment is well documented.<sup>2-4</sup> In one series, 67–90% of couples would prefer to have twins and 64% rejected any fear regarding multiple pregnancies.<sup>2</sup> In another series, 79% of couples wished to have two embryos transferred in their future *in vitro* fertilisation (IVF) treatment cycle with the attendant risks of multiple pregnancies.<sup>3</sup> Factors that have been associated with this wish for multiple pregnancies include nulliparity, lower family income, being younger, a longer period of infertility and a lack of knowledge of the complications associated with twin pregnancies.<sup>4</sup> To subfertile couples, twins from a single IVF cycle may be equivalent to having 'two babies for the price of one'. For these couples, having twins may come with some apparent advantages. Highlighted below are compelling reasons why subfertile couples may choose to have twins:

## Financial costs of ART

In the UK, the majority of IVF treatment is self-funded. Despite recommendations by the National Institute for Clinical Excellence (NICE) in 2004, state funding for IVF in the UK remains sparse, with extreme regional variation.<sup>5</sup> Where funding is available this is usually restricted to one cycle per couple. The financial costs of IVF range from £4000 to £8000 per cycle, dependent upon the clinic of choice. With

only one in four couples on average achieving a live birth in their first treatment cycle, couples requiring multiple cycles of IVF usually end up with a substantial bill. When other hidden costs are added, including the cost of lost labour when couples take time off work to attend clinics,<sup>6</sup> the huge financial cost of IVF may explain the desire for couples to get more than one baby from each IVF cycle.

#### Emotional costs of ART

Couples undergoing IVF have been shown to suffer from increased stress, reduced optimism and greater changes to marital and social relationships, and physical discomfort.<sup>7</sup> These feelings may be compounded if the woman's initial treatment cycle fails.<sup>8</sup> Having twins may offer IVF couples who desire more than one child the opportunity to complete their family in one go, thus avoiding the emotional and psychological trauma of further treatment.

#### Physical costs of ART

This refers to the pain and nuisance from multiple and frequent injections. The side effects from the medications range from injection site pain and bruising, hot flushes, dizziness, nausea, breast tenderness, visual disturbances, abdominal bloating, ovarian cysts and the serious complication of ovarian hyperstimulation syndrome.<sup>9</sup> In addition, there are the uncertain risks of ovarian and breast cancer from ART.<sup>10</sup> A twin pregnancy may therefore appeal to couples as they would then have no need to undergo further treatment cycles, thereby minimising the risks associated with repeated exposure to these drugs.

#### Time-related costs of ART

IVF success rates per cycle classically show an age-dependent decline; while the live birth rate per fresh egg cycle for women aged 37 years and below is over 30%, it declines to about 15% in women aged between 38 and 42 years.<sup>1</sup> The average 37-year-old women may prefer to have twins in her first IVF cycle rather than return after the birth of her singleton for a second cycle with a 15% chance of success.

The second time-related cost to ART is the time required off work for both treatment and monitoring. A study from The Netherlands showed that on average 33 hours are taken off work.<sup>6</sup> The Employment Rights Act (1996) allows a woman time off work for antenatal and maternity leave only when she is pregnant.<sup>11</sup> Employees do not actually have a statutory right to take time off for their ART treatment. Moreover, ART is not 'deemed incapacity' for statutory sick pay (SSP) rationales.<sup>12</sup> Despite such regulations, ART can cause physical and psychological stress, thus it is down to the employer to then consider SSP on medical grounds. Although some employers [including the National Health Service (NHS)] have adopted a specialised policy that entitles their employees to a number of days paid leave per IVF cycle,<sup>13</sup> the vast majority of

employers do not have such policies, with patients taking unauthorised time off to attend clinics during IVF. The true cost of lost labour time taken during IVF is not fully known but expected to be significant and may justify getting two babies from one IVF cycle.

#### Why twins are undesirable

Although twins remain appealing to couples undergoing IVF treatment, the concept of 'buy-one-get-one-free' with regards to IVF twins is extremely misleading. As appealing as they may, twins come at a very high cost.

#### Maternal costs: complications associated with twins

Well known maternal complications of a twin pregnancy include spontaneous miscarriage, severe hyperemesis gravidarum, hypertension, pre-eclampsia, antenatal thromboembolism, primary and secondary postpartum haemorrhages, anaemia, gestational diabetes, preterm rupture of membranes, preterm labour and high Caesarean section rates with its attendant implications, among others.<sup>3 14–17</sup> Maternal death is said to be increased by two-fold when comparing mothers of IVF twins to mothers of IVF singletons.<sup>18</sup> Twin pregnancies have also been associated with increased psychological morbidity for the entire family unit.<sup>19–21</sup>

#### Fetal costs: complications of twins

There are unfortunately just as many detrimental effects to the babies as there are to the mother: IVF twin pregnancies are associated with a five-fold increase in neonatal death when compared with singleton pregnancies.<sup>16 22–24</sup> They are also associated with an eight-fold increase in low birth weight, a four-fold increase in cerebral palsy and an increase in congenital malformations, when compared with singleton pregnancies.<sup>16 22–24</sup> Furthermore, there is a 10-fold increased rate of admission to the Neonatal Intensive Care Unit (NICU),<sup>18</sup> which can have a negative effect on the crucial bonding process in the neonatal period. Twins on average spend 9 days more in the NICU than singletons,<sup>3</sup> with an intensive care stay of longer than 4 weeks more likely in IVF twins compared to IVF singletons.<sup>18</sup>

IVF twins, even when compared to naturally conceived twins, have been shown to have an increased risk of preterm labour and a higher Caesarean section delivery rate.<sup>25</sup> Furthermore, IVF twins have an increased incidence of neonatal complications including respiratory distress syndrome, pneumothorax, the need for mechanical ventilation, admission to the NICU, as well as a higher rate of cytogenetic abnormalities when compared to spontaneously conceived twins.<sup>26</sup> IVF twins have been found to be on average 230 g lighter than twins conceived naturally.<sup>25</sup>

#### Financial costs to the couple

The total cost of raising twins is higher than raising the same number of singletons, as the family's expenditure is immediate for two and over a short time period.

Robin *et al.* reported that 73% of couples were challenged with exceptionally difficult financial pressures subsequent to their multiple births.<sup>27</sup> Furthermore, it takes longer for the mother to return to her job after multiple births,<sup>28</sup> if she is able to do so at all, with consequent loss of earnings. This may contribute to the common postnatal tension seen between couples parenting twins.<sup>28</sup>

#### Relationship stress and family pressures

Couples parenting twins have been shown to have a higher incidence of relationship stresses and marital breakdown.<sup>21 27</sup> Hay *et al.* reported increased marital stress among couples parenting twins.<sup>21</sup> This can be multiplied when babies are born premature or disabled.<sup>19 21 28</sup>

#### Cost of IVF to the state

In 2002, twins from IVF cost the NHS an immense 14 million pounds.<sup>29</sup> The total direct costs to the NHS per IVF twin family, including both maternal and infant costs, are disproportionately higher than per IVF singleton family.<sup>29</sup> Multiple pregnancies after IVF account for over half of the direct costs of IVF pregnancies per year despite only representing a third of the total number of maternities. Such economic outflow is inevitable since these complicated pregnancies require extra antenatal monitoring, which is more likely to involve hospitalisation and multiple admissions, intensive intrapartum and postpartum surveillance, more interventions and increased neonatal care. Another study estimates the potential cost for medical complications post-multiple delivery, including caring for premature babies, to be over US\$1.5 million.<sup>19</sup>

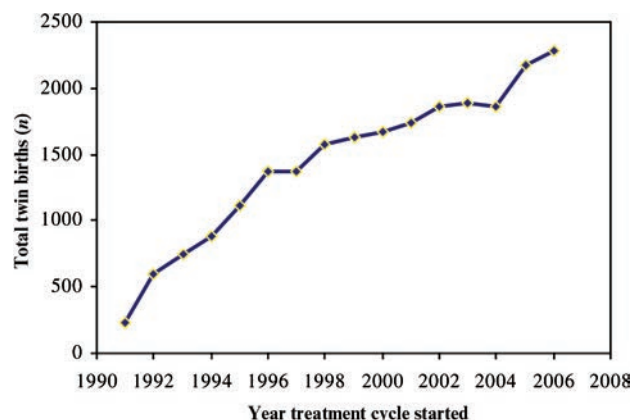
In the long term, IVF twins may also require increased social and special education services, with obvious cost implications on services.<sup>18</sup> It is for these reasons that multiple pregnancies are now considered one of the single biggest risks of IVF.

#### Reducing the incidence of IVF twins

In recent years, there has been a major drive to educate IVF patients, clinicians and other stakeholders about the implications IVF twins and the necessity for clinics to adopt strategies to minimise the incidence of multiple pregnancies resulting from ART. Summarised below are some established strategies to minimise ART twins.

#### Elective single embryo transfer

In 2001, the HFEA introduced a two-embryo policy that became mandatory by 2004; such that only a maximum of two embryos can be transferred in women below the age of 40 years with no exceptions.<sup>1</sup> This policy resulted in a significant drop in the number of triplet and higher-order pregnancies, but the twin pregnancy rates continued to rise<sup>18</sup> (Figure 1). Twin pregnancies are thought to occur in



**Figure 1** The increasing number of total twin births from 1991 to 2004 (Human Fertilisation and Embryology Authority register data).<sup>1</sup>

one in five IVF cycles compared to 1 in 80 couples who conceive naturally.<sup>1</sup>

In order to stem the rising trend of ART twins, the HFEA introduced a multiple birth target in 2009, requesting clinics to reduce the multiple pregnancy rate to a target level of 10% over a defined time period. All centres were asked to devise their own multiple birth minimisation strategy that would prevent them from exceeding this rate.<sup>1</sup> To facilitate this change in practice, a multidisciplinary stakeholder group was established, which worked to promote elective single embryo transfer (eSET) by developing tools to improve clinical practice, material to inform patients and health care professionals, and working with the Department of Health to remove potential barriers to implementing an eSET policy by improving NHS funding.<sup>30</sup> A Cochrane review, published in 2009, showed that the elective transfer of a single embryo resulted in fewer multiple pregnancies and a lower pregnancy and live birth rate compared to the transfer of two embryos. However, the cumulative live birth rate associated with a SET followed by a single frozen embryo transfer (FET) was comparable to that after one cycle where two embryos are replaced, while still maintaining a significantly lower multiple birth rate.<sup>31</sup> Data from a randomised controlled trial by Thurin *et al.*<sup>32</sup> are quite persuasive. The authors compared the transfer of two fresh embryos to the transfer of a single fresh embryo followed by a single cryo-preserved embryo, in women less than 36 years of age (i.e. good prognosis patients). The pregnancy rate resulting in at least one live birth was 42.9% and 38.8% for the respective groups, and the twin pregnancy rate was 33.1% and 0.8%, respectively. While eSET has been shown to be an effective strategy to minimise the number of IVF twins, some authors have cautioned on the need to limit eSET to younger women only, as results may be compromised if the policy is extended to include older women.<sup>33</sup> Scotland *et al.*, in their



modelling study, showed that the cost-effectiveness of double embryo transfer (DET) improved with age, and concluded that the decision to transfer two embryos may best be considered on a case-by-case basis for women aged 37–39 years.<sup>34</sup> It is therefore important that care be individualised and a blanket policy of eSET for all must be avoided.

The eSET policy remains one of the most effective ways to minimise the rate of IVF twins. This practice has become the norm in Scandinavian countries, leading to substantial reductions in multiple pregnancy rates without notably impacting on the cumulative delivery rates.<sup>35–37</sup> Early indications (as shown by recent HFEA data) are reassuring as the number of twins from IVF is showing a gradual but reassuring downward trend; a reflection of the impact of the recently introduced eSET policy (Figure 2)

The continuing success of this strategy is largely dependent on a number of other factors as discussed below.

#### Improvement in embryo selection

Embryo quality is consistently the most vital criterion for a successful eSET policy.<sup>18, 38</sup> The ability to confidently select the single best embryo in the cohort for transfer is vital for optimum pregnancy rates. The current cleavage stage embryo grading systems based on the observation of cleavage rates and morphology, number of blastomeres, evenness of cell division and degree of fragmentation<sup>38</sup> are not uniform, and relatively subjective. This remains a major challenge for reliable embryo selection at the cleavage stage. The British Fertility Society and the Association of Clinical Embryologists are currently in the process of developing a standardised grading system that could be used nationally.<sup>30</sup>

The development of new culture media, as well as increasing experience with extended embryo culture

to the blastocyst stage, potentially allows embryos to self-select, since only the more competent embryos will make it to the blastocyst stage,<sup>39, 40</sup> thus facilitating embryo selection for transfer. Implantation rates have been shown to be significantly higher with blastocysts compared with cleavage stage embryos.<sup>40, 41</sup> Where good quality embryos are available, the transfer of a single blastocyst on Day 5 shows a significantly higher pregnancy and live birth rate compared to the transfer of a single embryo on Day 3.<sup>40, 41</sup>

#### Better cryopreservation techniques

Optimum cryopreservation of suitable surplus embryos is an important part of the policy of eSET as it saves unused embryos for future use. Better cryopreservation techniques will mean better embryo survival and better pregnancy rates following the transfer of cryo-thawed embryos. Consequently, this will translate into a good cumulative pregnancy rate, thus encouraging couples to elect for eSET. The current technique of vitrification has been shown to give better results than the slow freezing method of embryo-cryopreservation.<sup>42</sup>

#### Adequate state funding for ART

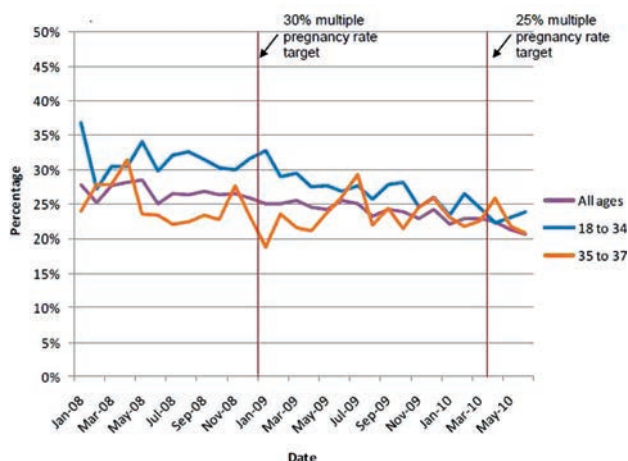
The NICE guidelines recommend the provision of three fresh IVF cycles with cryopreservation of suitable remaining embryos and subsequent FET cycles.<sup>43</sup> In the UK, a major obstacle to the uptake of eSET remains the fact that in practice the NICE guidelines are rarely implemented by primary care trusts (PCTs). This ultimately means that the majority of IVF cycles are self-funded.<sup>5</sup> To promote eSET, public funding will need to be increased, not only to fund fresh cycles, but also to fund the subsequent transfer of cryo-preserved embryos. Some PCTs are now providing funding for FET cycles to encourage eSET.<sup>5</sup> Although this may seem expensive in the short term, the costs will be offset by long-term benefits if multiple pregnancies and their consequences are avoided. It has been proposed that if the financial burden is removed, couples undergoing IVF would be more willing to accept eSET.<sup>38, 44</sup>

#### Redefining IVF success

It has been suggested that regulatory authorities may be able to encourage the uptake of eSET by refining the way in which success rates are presented. Success rates should incorporate the degree of morbidity and total costs involved in achieving a live birth. The aim of IVF treatment should be to achieve a full-term singleton birth with minimum treatment burden.<sup>18</sup>

#### Educating the couple

When couples are counselled adequately they are more likely to consider eSET.<sup>45</sup> General practitioners are in an ideal position to be able to transmit background information to couples seeking fertility treatment. They are more likely to provide information about the processes and risks accompanying ART in an unbiased



**Figure 2** Multiple pregnancies as a percentage of all pregnancies; January 2008–June 2010 (Human Fertilisation and Embryology Authority register data).<sup>1</sup>

manner, thus enabling couples to weigh up the pros and cons in order to make an informed decision.

### Educating fertility clinicians

The desire to secure good 'league table positions' may influence clinicians' attitude towards eSET. Clinics that chose to continue to transfer two embryos to increase their pregnancy rates are doing so at the risk of producing twins, and they must remember the need to consider the welfare of the unborn children; as required under Section 13 of the Human Fertilisation and Embryology Act. Welfare in this context includes maximising the chances of producing a full-term healthy neonate.<sup>18</sup>

### Conclusions

Multiple pregnancies remain a major complication of ART. The risks associated with multiple births are very much underappreciated by IVF couples who continue to want twins. Such couples may put forward good reasons why IVF twins may be desirable; such reasons may not, however, justify the adverse effects of multiple pregnancies on the babies, their mother, the family and the health system. Assisted reproduction practitioners should aim to achieve a live birth with minimum medical, physical, emotional, psychological and financial costs to the couple and the health system. The aim of IVF treatment should be to achieve a full-term singleton birth with minimum treatment burden. Reducing the incidence of ART twins remains a major challenge towards this goal and the elective transfer of one embryo at a time remains the most effective strategy in the good prognostic age group.<sup>46</sup> However, in implementing the policy of eSET, it is important that each case be assessed on an individual basis, where DET may be more cost-effective in the older age group.<sup>37</sup> Adequate and continuous education of the patients, the public and funding authorities is essential if the policy of eSET is to be successfully implemented in the UK.

**Competing interests** None.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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## FACULTY AWARDS

The Faculty of Sexual and Reproductive Healthcare has available a number of annual awards for which applications are invited from Faculty members and non-members as listed below. Details of the individual awards, together with an application form and/or guidelines on how to apply and any eligibility criteria, may be found on the Faculty website at [www.fsrh.org](http://www.fsrh.org).

### Margaret Jackson Prize Essay

**Award:** Three prizes awarded annually for the best essays on a topic related to contraceptive, reproductive and sexual health care. The first prize is £300, with £100 each for the two runners-up.

**Eligibility:** Individuals (undergraduate medical students)

**Closing date:** 24 March annually

### The David Bromham Annual Memorial Award

**Award:** Prize awarded for a piece of work which, through inspiration, innovation or energy, has furthered the practice of sexual and reproductive health care in any way and any setting.

**Eligibility:** Individuals (Faculty members) or teams

**Closing date:** 7 April annually