

One child at a time

Reducing multiple births after IVF

Report of the Expert Group on Multiple Births after IVF

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Chair's Foreword

Multiple pregnancy is a major cause of stillbirth, neonatal death and disability. Compared with singletons, twins are four times more likely to die in pregnancy, seven times more likely to die shortly after birth, ten times more likely to be admitted to a neonatal special care unit, and have six times the risk of cerebral palsy. Maternal morbidity and mortality is also increased due to late miscarriage, high blood pressure, pre-eclampsia, and haemorrhage amongst others.

As obstetricians and gynaecologists we strive for a healthy outcome for every mother and child, and so much of this hurt is avoidable. Up to half of all multiple pregnancies result from various forms of fertility treatment; at least a quarter of all twins and most triplets are caused by clinicians replacing too many embryos during IVF procedures. It saddens and frustrates me to see that so many children born after fertility treatments are denied the best start to life.

Having been involved in maternity and fertility services for over thirty years, I have come to understand the deep desire of couples for a family, and the emotional and financial pressures created by the underfunding and inequity of fertility services in this country. Every week at work I meet couples who are willing to try everything in order to achieve the one thing they want most: their own child.

I am now convinced that with advances in fertility treatment, and with the benefit of the experience in some European countries of transferring only one embryo to many fertility patients, it is time to make the change: International data shows that the incidence of twins after IVF can be reduced without damaging women's chances of conceiving.

I have been privileged to chair an extraordinary group of experts, assembled in response to a request from the HFEA to gather information about multiple births after IVF treatments, and to recommend ways that this problem may be addressed. The committee comprised paediatricians, reproductive medicine specialists, embryologists, health care commissioners, specialist nurses and involved lay members, all of whom contributed to the quality of this report. I am particularly grateful to advisors from abroad (Jan Gerris, Karl Nygren, Didi Braat, Lena Gimbergsson) who have explored and successfully implemented new policies in their own countries, and who gave us of their time so willingly. I also wish to thank Juliet Tizzard, Charlotte Augst, Vishnee Sauntoo, Tim Whitaker and David Tellis from the HFEA Executive for their considerable help in the meetings and in drafting this report.



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Executive Summary

Multiple birth is the single biggest risk to the health and welfare of children born after in vitro fertilisation (IVF). It can be effectively reduced by transferring only one embryo to those women who are most at risk of having twins. The time has come to make this change to IVF practice in the UK.

This report is the outcome of a series of discussions the Expert Group on Multiple Births after IVF has had since the autumn of 2005. The Human Fertilisation and Embryology Authority (HFEA) set up the independent expert group in response to rising concerns about the incidence of multiple births after IVF/ICSI

(*in vitro* fertilisation and intra-cytoplasmic sperm injection). The group reviewed the available international and national data on multiple births after IVF, health and psychosocial outcomes for twins and their families, and the experience with single embryo transfer gathered in some European countries. It makes recommendations to the HFEA and other organisations that have a role to play in reducing the high incidence of multiple births after IVF.

The most important findings of the group are summarised below.

Incidence of multiple births after IVF/ICSI

- Currently, about 1 in 4 IVF pregnancies leads to the birth of twins. The risk is more than ten times higher than would be expected after spontaneous (natural) conception.
- The number of IVF triplets has decreased significantly since HFEA guidance on two-embryo transfer was tightened.¹
- Although the incidence of identical twinning is also increased after IVF, most IVF twins are non-identical, i.e. they come from two different embryos that were simultaneously transferred to and implanted in the woman's womb.
- Non-IVF fertility treatments (for example IUI – intra uterine insemination) also lead to increased multiple pregnancy rates, but the exact incidence is harder to estimate since these treatments and their outcomes are not registered centrally.

Problems of multiple pregnancy and birth

- Twin pregnancies carry much higher obstetric risks for women: miscarriage, pre-eclampsia, gestational diabetes, haemorrhage and instrumental delivery are all much more common in women carrying twins.
- The biggest risk factor for twins is prematurity and low birth weight, which often necessitates hospitalisation at the beginning of life, and is linked to a significant risk of neonatal death of one or both twins, beside longer term health and cognitive effects. For example twins are at least six times more likely than singletons to suffer from cerebral palsy.

- There are also well-documented problems for families of twins that range from financial hardship to a higher incidence of maternal depression and marital problems.

All these risks are well documented and can no longer be ignored.

Redefining success

- A multiple pregnancy should not be regarded as the ideal outcome of IVF treatment. The problem is not that two healthy babies might be born, but that too often adverse outcomes occur for the mother and one or both of the babies.
- IVF clinicians, embryologists, nurses and counsellors, the professional bodies, patient organisations and IVF patients themselves need to acknowledge that IVF children (like all other children) are entitled to the best possible start in life: their chances of being born as full term singletons with a normal birth weight need to be maximised.

Elective single embryo transfer (eSET) for good-prognosis IVF patients

- The only way to reduce the multiple birth rate after IVF is to transfer only one embryo to those women at most risk of having twins. Overall, eSET needs to be made the norm in IVF treatment.
- International datasets show that single embryo transfer policies can be introduced without significantly reducing pregnancy rates by targeting good prognosis patients (for example relatively young women, women who have not had a number of previous failed IVF attempts), and by ensuring effective embryo freezing programmes.
- The decision as to how many patients should receive one embryo, is a balance between twin rate and success in achieving a pregnancy. Based on large national data sets we conclude that offering eSET to around 50% of IVF patients will lead to a twin rate of less than 10%. This is, for now, an acceptable balance between reducing the number of twins born after IVF and maintaining IVF patients' chances to conceive.
- In order to maintain pregnancy rates it is important that effective cryopreservation programmes accompany eSET, such that good quality additional embryos are frozen and available for transfer should the fresh eSET cycle be unsuccessful.
- Where more than one good quality blastocyst is available for transfer on day 5 or 6 of culture, the case for single blastocyst transfer is overwhelming.

Difficulties for making the transition

We are aware that making this transition is not going to be easy. There are obstacles to progress, but these can and must be overcome in order to make treatments safer for IVF patients and their children.

- Those countries that have introduced eSET policies successfully all have fertility sectors that work differently from the UK: generally patients have better access to publicly funded IVF treatments, which directly influences patients' attitudes to eSET, and their patient profile may be different to the UK. Nevertheless, even if the international evidence is not wholly transferable to the UK, the broad trends are helpful in modelling what is likely to happen in the UK context.
- The failure to implement fully the National Institute for Health and Clinical Excellence (NICE) clinical guideline on fertility treatments in England and Wales (and the equivalent rationing of NHS fertility services in Scotland and Northern Ireland), and the consequent lack and inconsistency of NHS funded IVF in the whole of the UK, is the single greatest obstacle to the introduction of eSET policies in the UK.
- The refusal of many Primary Care Trusts (PCTs) to include cryopreservation in a funded cycle (as required by NICE) further exacerbates the problem. Patients and their clinicians are likely to resist even the smallest reduction in pregnancy rates if they believe that this is their sole chance of a pregnancy.

Recommendations for the HFEA

The continuing escalation in twin births means that the status quo is no longer an option. In order to change the practices of the UK fertility sector quickly and consistently, new HFEA guidance on embryo transfers is required urgently. Based on the previous experience of limiting the number of embryos for transfer to two, we do not see that professional guidelines alone can convince the sector of the need for change.

We have identified two main policy options for the HFEA to consider, both are based on the assumption that eSET cycles should be the norm for IVF:

- Setting clinics an overall maximum proportion of twin births that should not be exceeded (for example 5 to 10%), which can be achieved stepwise over time;
- Setting criteria for the group of patients (those with the best prognosis and thus the highest risk of multiple pregnancy) who should be offered eSET cycles in the first instance.

The HFEA collects and publishes information about IVF treatment outcomes ('success rates'). These results are inevitably taken by patient, media and public bodies as league tables. The presence of league tables has a strong effect on the practice of IVF in the UK. Clinics tend to transfer higher numbers of embryos to achieve the highest possible success rates. The flow of patients to both the private and NHS sectors is influenced by the position of clinics in the league table.

Furthermore, the way this data is collected and reported – separating live births per fresh cycle started from frozen follow-on cycles, rather than combining the two into cumulative birth rates per egg collection – does not ease the transition to eSET. League tables do not take regard of the different patient populations clinics might serve, nor do they acknowledge the adverse impact of multiple pregnancies.

- We recommend that the HFEA evaluate how better to collect and publish outcome data for the UK sector in order to represent the incidence of multiple births as a complication, rather than a success, and to reduce incentives for widespread use of double embryo transfer. For example, it could consider publishing cumulative birth rates including frozen follow-on cycles in order to encourage the transition to eSET as the norm.

Recommendations for other organisations

Progress will be difficult if the HFEA acts in isolation. Other key organisations have an important role to play in assisting the transition to safer IVF based on eSET.

Clinicians and IVF professionals

IVF professionals need to acknowledge the problems they create for some IVF children and their families by their continued use of multiple embryo transfer and the subsequent high incidence of twins.

- Clinics should audit their data in order to identify the patients and embryos with the highest chance of conceiving / implantation and thus the highest risk of multiple pregnancy.
- They should develop good patient and embryo selection protocols for eSET cycles and need to offer effective cryopreservation programmes.
- They should educate themselves about the incidence and significant risks of multiple pregnancy, and need to communicate these risks clearly to their patients.

The NHS

NHS commissioners need to address the inconsistencies and overall lack of access to the recommended three full (fresh and frozen) cycles of IVF in order to take the pressures out of the UK fertility sector that distort best practice and limit patient choice.

- Since the public health burden of multiple birth falls on the NHS and then other publicly funded services, commissioners should consider the potential savings (for example in neonatal intensive care – a notoriously overstretched service) that could be realised were more IVF patients offered eSET cycles.
- The twin rate of clinics should be taken into account when the NHS commissions fertility services.
- A statement from the Department of Health about the public health benefits of eSET and subsequent lower twin rates, and clarity on the priority to be ascribed to NHS funded IVF services, would help to raise awareness and a sense of urgency amongst local commissioners.

The professional bodies and patient groups

- The professional bodies (British Fertility Society, Association of Clinical Embryologists, Royal College of Obstetricians and Gynaecologists) should work together to provide guidelines that would help clinics identify which patients and which embryos are most appropriate for eSET.
- Clinicians, counsellors, Royal College of Nursing fertility nurses, the Multiple Births Foundation, patient groups like Infertility Network UK and the HFEA itself need to evaluate and improve patient information about the risks of multiple pregnancy and birth.

Understanding the background

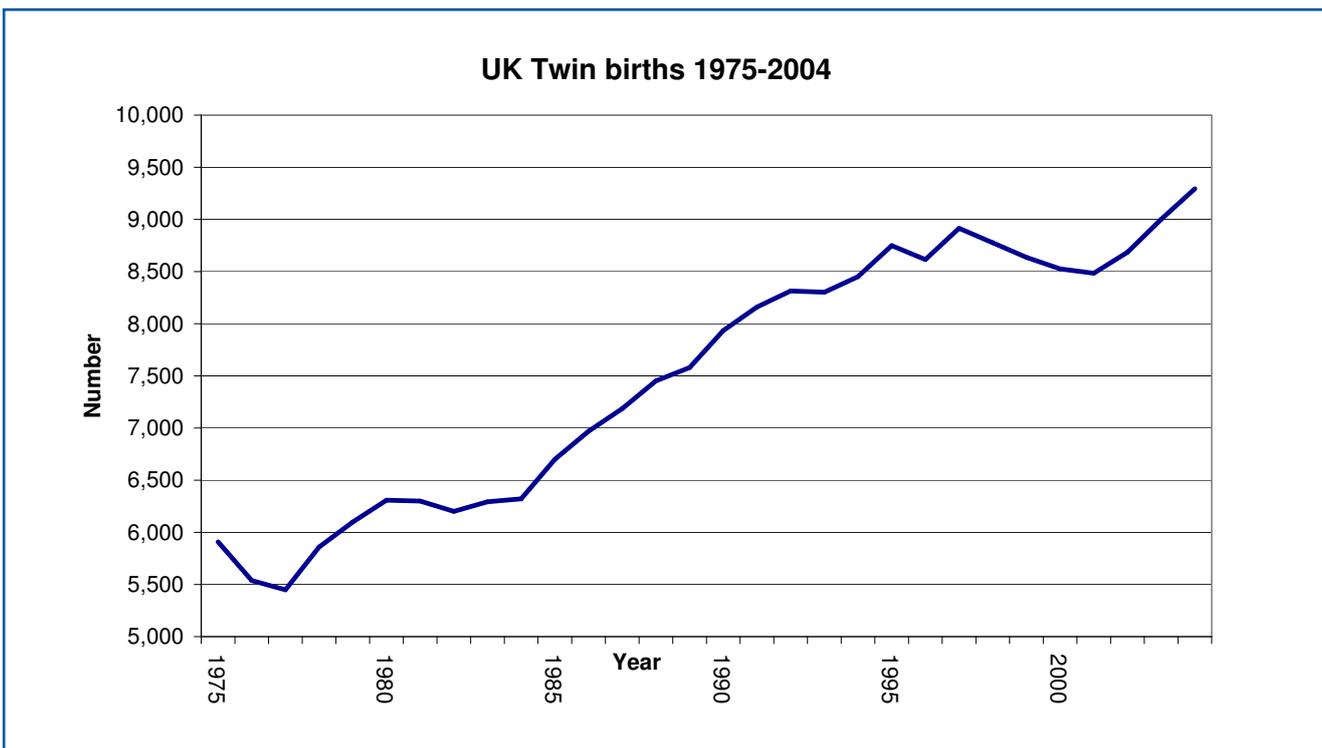
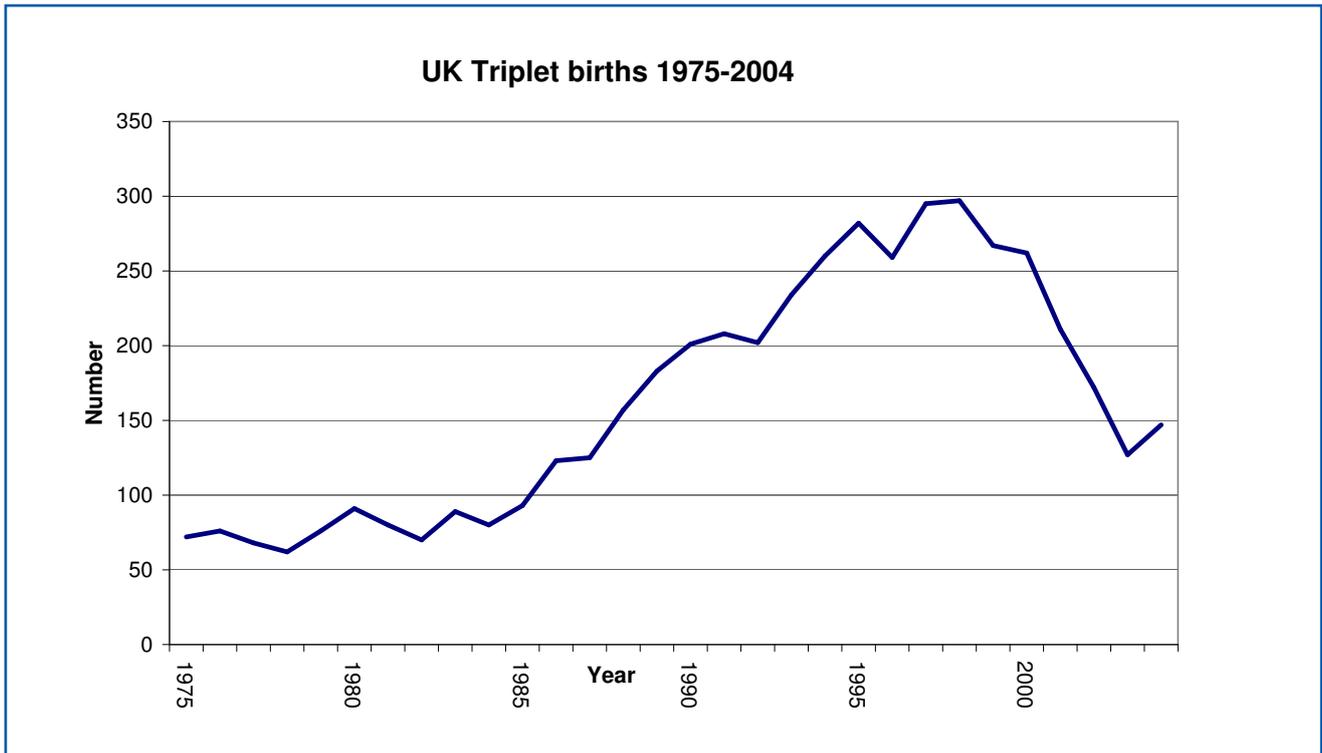
This section sets out the parameters and history to the Expert Group's work and explores the context in which the HFEA has to address the problem of multiple births after IVF.

1. Introduction

- 1.1 The multiple birth and single embryo transfer (MBSET) Expert Group was convened in 2005 in order to advise the Human Fertilisation and Embryology (HFEA) Executive on the risks of multiple births after assisted conception techniques. The group was set up in the context of a rising twin birth rate accompanying the increased successful use of assisted reproductive technologies (ART) – about one quarter of pregnancies after *in vitro* fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI) are twins.²
- 1.2 Over the past years, the HFEA has taken a number of steps to encourage licensed centres to reduce the incidence of multiple births following IVF and ICSI. Since the first *Code of Practice* was published in 1991, it has expected centres to transfer no more than three embryos in any one IVF cycle.
- 1.3 With the incidence of triplet births still relatively high, the HFEA introduced a two-embryo policy in August 2001 (Chair's Letter 01(10)). This policy expected centres to transfer a maximum of two embryos, except in exceptional circumstances, when three embryos could be transferred. As compliance was still sporadic, in March 2004, when the Authority published the sixth edition of the *Code of Practice*, the policy was tightened further, so that a maximum of two embryos could be transferred to women under the age of 40 – with no exceptions – and a maximum of three transferable to women aged 40 and over.
- 1.4 These measures effectively halved the number of triplets born in the UK, but had no effect on twin births which continued to rise.³ Although triplets have a very high relative risk of being born very prematurely and with a low birthweight (90% of triplets are born under 37 weeks of gestation or under 2500g at birth),⁴ they now account only for a small proportion of pre-term and low-birthweight newborns. Around 1 in 4 twins born in the UK is the outcome of IVF treatments;⁵ taking into account all assisted conception techniques, the proportion of ART twins is much higher (estimated around 1 in 2). Twins also make up a significant proportion of pre-term and low-birthweight newborns. They account for between 10% and 20% of all premature and low-birthweight babies.⁶ About half of twins are born under 37 weeks of gestation or under 2500g at birth.⁷
- 1.5 Office of National Statistics data clearly shows the rise in multiple births over the last three decades. The steep rise in the incidence of triplet births slowed and eventually fell from 2001 with a change in HFEA policy that instructed that two embryo transfer should be the normal maximum. The incidence of twin births continues to rise.
- 1.6 The group has met on six occasions since October 2005. It has reviewed and discussed:
 - Outcome data for twin and higher order births;
 - Data on the impact of multiple births on children's and neonatal services;
 - The international experience of moving towards elective single embryo transfer (eSET) policies;
 - Patient perspectives on eSET;
 - Information about the commissioning and funding of IVF by the NHS;
 - Ways of presenting ART outcome data that might encourage the use of eSET;

- Possible policies for the reduction of multiple pregnancies;
- Legal advice regarding various policy options.

1.7 A consensus emerged on a wide range of issues during the course of our discussions. This report presents our shared understanding of the problem and discusses possible difficulties for making progress. The report concludes with a list of policy recommendations.



2. Policy objectives

2.1 We agreed a number of objectives for any policy that should be adopted. Ideally any policy should aim to achieve the following:

- The number of multiple births following IVF is reduced, thereby reducing the morbidity and mortality of mothers and babies and the pressure on NHS children's services;
- The overall cost of treatment for patients does not increase significantly if more cycles are needed;
- Live birth rates per stimulation cycle started are maintained as far as possible;
- Other aspects of patient care are not compromised;
- The doctor/patient decision-making process is respected;
- The HFEA is not drawn unnecessarily into the autonomy of clinical decisions;
- Clinics develop better embryo selection practices.

Multiple pregnancies – the facts

After natural conception, the chance of a multiple pregnancy is between 1 and 2% (spontaneous multiple pregnancy).⁸ After ICSI/IVF currently around 24 % of pregnancies are multiple.⁹ The incidence of multiple pregnancy after other types of fertility treatment is harder to assess because (unlike techniques involving fertilisation outside the woman's body) they are not centrally registered. However, the twinning rate after non-IVF assisted conception is also significantly increased.¹⁰

There are different types of multiple pregnancies:

- **Dizygotic twins (non-identical twins)** arise when two eggs are fertilised (two zygotes) and implant in the woman's uterus. These non-identical twins are no more alike than other brothers and sisters.
- **Monozygotic twins (identical twins)** arise when a single egg is fertilised – one zygote. This egg splits into two, creating twins who have the same genes as one another. They may share a placenta or may have one each.
- **Higher order pregnancies (triplets or more)** can arise from one, two, or more fertilised eggs implanting in the uterus and developing into babies.

If a woman is pregnant with only one fetus it is known as a **singleton pregnancy**, and the baby is called a **singleton**.

Most twins after fertility treatment are dizygotic. This is because more than one egg is fertilised or more than one embryo is transferred to the woman. However, research has shown that the risk of identical twinning is also increased (2 to 5 times higher)¹¹ in women receiving fertility treatments. The reasons for this are not known, but may include longer culture *in vitro*, assisted hatching, and pre-implantation biopsy for genetic diagnosis/ screening (PGD/PGS). This means, for example, that a woman can become pregnant with triplets, although only two embryos were transferred, or can find herself pregnant with twins, although only one embryo was transferred.

The **chorion** is the outer sac or membrane which surrounds the baby and the placenta.

- **Monochorionic twins** have one chorion and share a placenta which carries a higher risk for the babies during pregnancy and birth. This can only happen when the twins are monozygotic (identical) because they arise from a single embryo splitting into two.
- **Dichorionic twins** have their own placenta and gestational sac.

Many of the risks of multiple pregnancy are higher for monochorionic twins than for dichorionic ones. For example the risk of congenital malformations is significantly increased for monochorionic twins, but does not seem to be much increased for dichorionic ones.¹² Similarly, the risk of cerebral palsy is higher for twins that had to share a placenta in the womb.¹³ If twin fetuses share the placenta, a condition called twin-twin transfusion syndrome may develop if the blood flow between the babies becomes unbalanced.

Because most IVF twins are dizygotic (i.e. come from two different eggs) and therefore dichorionic, they are less affected by the risks that result from sharing a placenta. However, since **the biggest risk for twins (IVF or naturally conceived) is prematurity and low birthweight, these affect identical and non-identical twins equally.**¹⁴

Because multiple pregnancies carry a higher risk for mothers and babies, a recent Royal College of Obstetricians and Gynaecologists (RCOG) study group recommended that women who are pregnant with twins or more should receive their antenatal, obstetric and perinatal care in specialist settings (twin clinics) that can manage the increased risks of multiple pregnancies. However, currently care is not consistent across the UK. There is also no routine financial or social support made available to parents of newborn twins or even triplets.

There are two national organisations that can provide more information and support on the issue of twins.

- **The Multiple Births Foundation (MBF)** Tel: 020 8383 3519 www.multiplebirths.org.uk
- **Twins and Multiple Births Association (TAMBA)** Tel: 0870 770 3305 www.tamba.org.uk

3. The international experience with reducing multiple births after assisted conception

3.1 The high incidence of multiple births after assisted conception, particularly after IVF, has been identified as a problem internationally. Countries have adopted different strategies to address this. Broadly speaking, Northern European, in particular Scandinavian, countries have led the way towards wider use of eSET as a strategy for reducing multiple pregnancies, with Southern Europe and the United States not (yet) taking up this approach.¹⁵ The international situation is compared in the table below.

Multiple births after ART – international perspectives

Country	Policy	Comments
United Kingdom	From 2003, the HFEA limits the number of embryos for transfer to 2 in women under 40, and to 3 for older women.	Initially, more flexible guidance failed to achieve the desired effect of clearly reducing the incidence of higher order pregnancies. Since the introduction of the new guidance, the incidence of triplets has reduced, but the number of twins continues to rise.
Belgium	Introduction of a reimbursement system that links funding for 6 IVF cycles per patient to the compulsory use of eSET in the first cycle in women <36 years, use of eSET in follow-on cycles depends on age and embryo quality. Embryo rating is left to clinics.	Virtually complete avoidance of triplet births; twin births have dropped to around 7% without a significant decrease in pregnancy rates.
Finland	No state regulation, but the sector has moved successfully to wide-spread use of eSET with follow-on cryopreservation.	Virtually no IVF triplets, IVF twin rate has dropped significantly; visible impact on national birth registry, overall pregnancy rates remain unchanged.

Sweden	Regulation by the National Board on Health and Welfare states that in principle only one embryo should be replaced apart from exceptional circumstances, which seem to be loosely defined. ¹⁶	In practice 70% of all IVF cycles are now eSET cycles. Pregnancy rates have been maintained and the twin rate has reduced to around 5%.
Norway and Denmark	No state regulation, but the sector has moved to a substantial proportion of eSET cycles.	Swedish, Norwegian and Danish groups have collaborated in a number of multi-centre trials and have shown good success rates for eSET cycles.
Netherlands	Dutch fertility sector introduced eSET policies without state legislation.	Significant proportion of cycles now eSET, but Government decision to withdraw funding from the first IVF cycle for each patient might impact negatively on patient attitudes towards eSET (and clinical practice).
Germany	Embryo Protection Act 1990: No more than 3 oocytes can be cultured beyond the two-pronucleate stage, embryo selection practices disallowed, no cleavage stage embryos can be frozen, so all embryos need to be transferred.	Hinders effective embryo selection. Very high triplet and twin rate.
Switzerland and Austria	Similar situation to Germany.	

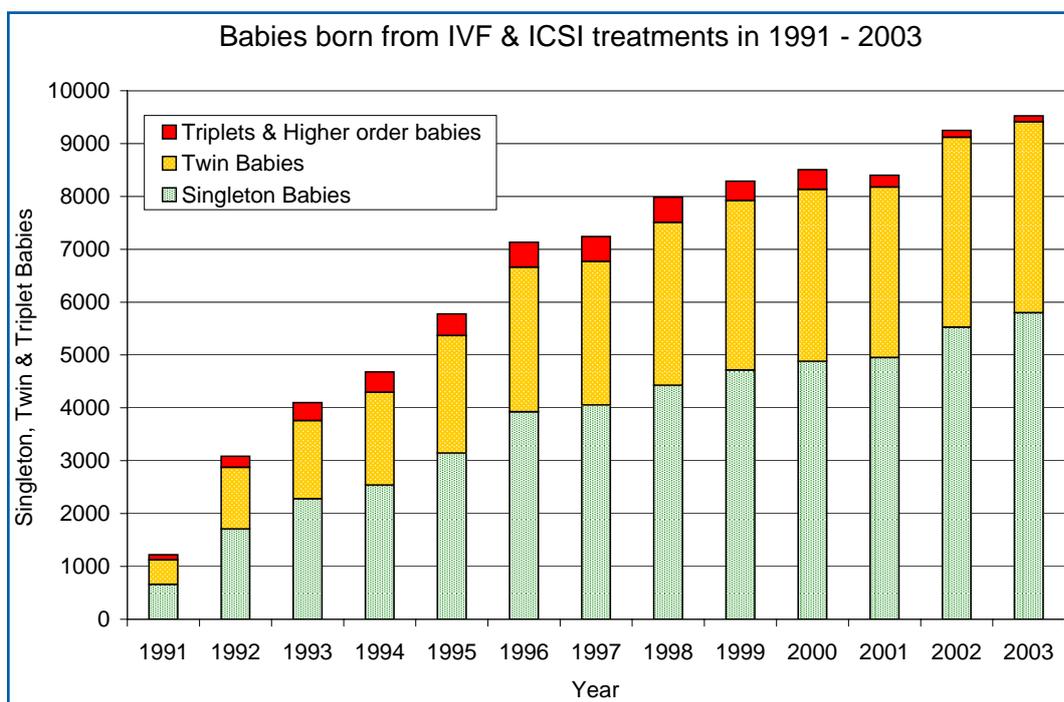
Italy	Recent legislative change: Only three eggs can be fertilised, all the embryos need to be implanted.	Makes eSET difficult. Problem of triplets is re-emerging in centres that had virtually eliminated it.
Southern European Countries (France, Spain, Portugal, Greece)	No legislation or regulations on reducing numbers of multiples, no evidence of rising number of eSET cycles.	
United States	No regulation, but 1999 Guidelines by the American Society of Reproductive Medicine (ASRM) advise no more than 2 embryos for good prognosis women, no more than 5 for poor prognosis patients.	In recent years a downwards trend in higher order multiples has been noted, but number of twins seems to continue to rise. Role of fetal reduction in cutting multiple rates unclear.

- 3.2. Several European Society of Human Reproduction and Embryology (ESHRE) working groups have addressed the problem of multiple births and have recommended the wider use of eSET cycles to reduce the number of premature and sick twins after IVF/ICSI.¹⁷ The Bertarelli Foundation also held a meeting of international leaders in the field of reproductive medicine in order to improve education on the risks of multiples and to reduce their incidence.¹⁸
- 3.3 Internationally there is a strong move towards more extensive use of eSET in ART based on an increased awareness of the human costs of the high incidence of multiple births after ARTs. The UK is an influential country in the international context, its decision on multiple pregnancies will be watched with interest. It has an internationally respected regulator and a bigger and more diverse provider sector than some of the Scandinavian countries. The paucity of public sector funding has meant that fertility services operate in a more market driven way, with most IVF treatments paid for privately by the patients. We believe that if the UK moved towards wider use of eSET cycles, this would send an important signal out to the European sector as a whole. It might accelerate international acceptance of eSET strategies.

4. A range of measures and a range of responsibilities

- 4.1 We believe that the problem of multiple births cannot be solved by the HFEA alone, and requires a change in mindset of all the involved parties. A whole range of organisations and individuals need to tackle aspects of the problem. We decided to develop policy recommendations not just for the HFEA, but also for the other organisations that need to become part of the solution.
- 4.2 Apart from the HFEA, these include:
- Clinics and clinicians;
 - The professional bodies (for example RCOG, ACE, BFS, RCPCH, BICA, RCN fertility nurses);
 - Patient groups;
 - NHS commissioners;
 - The Department of Health and the devolved departments across the UK;
 - NICE;
 - Academics and researchers.
- 4.3 Furthermore, the group agreed that the HFEA itself, in order to develop credible and coherent policies on multiple births, needed to address the issue across its various functions in an integrated way through:
- Reviewing, developing and issuing formal guidance to clinics;
 - Its inspections, its risk management, and in liaising with clinics on a day-to-day basis;
 - Its communication with patients and other stakeholders, including through the HFEA's presentation of outcome data;
 - Advocating beneficial policies to all involved.

Understanding the problem



Number of singleton, twins and triplet born following IVF/ICSI procedures in the UK (HFEA register data)

As the graph above shows, over 3600 twins were born as a result of IVF treatments in 2003, excluding those lost as late miscarriages. We are all in agreement that the number of multiple pregnancies resulting from IVF technologies is unacceptably high and needs to be reduced significantly. The advisory group agrees with the European Society of Human Reproduction (ESHRE) Ethical Taskforce assessment that 'there are far too many multiple pregnancies, with their intrinsic risk for the resulting children' and that the 'goal of medically assisted procreation must be a singleton pregnancy'.¹⁹

In the UK, about 1 in 4 IVF pregnancies (23.6%)²⁰ results in a multiple birth. Iatrogenic (medically induced) multiple births are a problem for a number of reasons. They can cause:

- Health risks for the children themselves;
- Health risks for the mothers;
- Psychosocial problems for the families of twins;
- Pressure on neonatal and children's services.

5. The health risks for twins

- 5.1 Amongst twins, all the major risks of morbidity and mortality are significantly increased.²¹ Most of the health problems of twins can be explained by their frequent prematurity and their lower gestational weight.²² As a rough estimate, IVF twins are born with an average gestational age 3 weeks less than IVF singletons and with a mean birth weight ranging between 800g and 1000g less.²³ However, many IVF twins are born much smaller and earlier than these average figures suggest.²⁴
- 5.2 The risk of death around the time of birth (perinatal death) is between 3 to 6 times higher for twins and nine times higher for triplets compared with singletons.²⁵ National data on all the babies born in the year 2001 in Australia shows that multiple birth is the biggest cause of neonatal death (death within the first 28 days of life), outnumbering deaths after placental separation and haemorrhage, respiratory distress or heart defects.²⁶
- 5.3 Also, the rate of cerebral palsy is at least six times higher for twins and 18 times higher for triplets than for singleton babies.²⁷ Cerebral palsy is caused by irreparable damage to parts of the brain. One cause of this condition is lack of blood supply and thus lack of oxygen to the brain before, during or after birth. Cerebral palsy results in poor muscle control. It sometimes also affects cognitive development or intelligence. Both the movement and cognitive problems can range from barely noticeable to severe. It is not progressive (i.e. it does not get worse), but it is sometimes not diagnosed until some months or even years after the birth because it can become more apparent as the child gets older.
- 5.4 One recent Swedish study comprising 11 fertility centres and 661 patients found that one third of children born after double embryo transfer suffered severe neonatal complications, requiring neonatal care in hospital.²⁸ A smaller British study found that IVF twins were more than 10 times more likely to have been admitted to a special care baby unit than singleton IVF babies.²⁹ A national cohort study on all the IVF twins born in 1997 in Denmark found that IVF twins were twice as likely to be admitted to neonatal intensive care units than IVF singletons (39.9% and 18.9% respectively).³⁰ Intensive care stays of more than four weeks were endured by 11.7% of IVF twins, but only 1.6% of IVF singletons. Mothers of IVF twins reported higher rates of surgical intervention, disability and special needs for their children than mothers of singletons. Twice as many IVF twins than singletons needed speech therapy (6.4 vs. 3.2%). The differences disappeared after stratification for birthweight and prematurity, indicating that the less positive outcomes for twins could be entirely explained by their prematurity and low birth weight.
- 5.5 There is substantial evidence documenting the risks of prematurity. The UK's leading study on extreme prematurity³¹ found that 3 in 4 babies born before 26 weeks died very soon after birth and before admission to intensive care. Overall survival of those who were admitted was 39%. 62% of the survivors had significant brain damage, retinopathy of prematurity (eye damage), and/or ongoing oxygen dependence at their predicted due date. These would result in physical and/or mental impairment. The authors suggest that fertility treatments are the likely cause of the high proportion of multiples in the study group. In a recent literature review on neurological development of twins, Professor Neil Marlow confirms the clear correlation between gestational age and cognitive abilities or IQ. A

lower IQ which has also been clearly linked to attention deficit hyperactivity disorder and behavioural difficulties will persist into later life.³²

- 5.6 Children born between 26 and 32 weeks will also need admission to neonatal intensive care units. There is still significant mortality and morbidity at these gestations. After 32 weeks perinatal complications are rarer but still occur and special attention will be needed in the neonatal period. Even these more mature babies may have educational and behavioural difficulties, with 1 in 4 of those born between 32 and 35 weeks requiring extra educational support at school when they are 7 years old.³³
- 5.7 Finally, a recent study by Oakley and Doyle³⁴ attempted to estimate the contribution of multiple births after IVF to perinatal mortality in the UK in a given year. It found that, if all children born after IVF had been singletons or spontaneously occurring monozygotic twins, 73 perinatal deaths (deaths occurring immediately around the week of birth) in the year 2001 alone would have been avoided. The incidence of disability and long-term ill-health will be by far greater than the relatively small risk of mortality after multiple births. Including all fertility treatments (including IUI), the authors estimate that at least 220 deaths were attributable to the excess risk of multiple births after assisted conception in the same year. If this number of newborns died from hospital acquired infection, this would be treated as a major medical scandal.
- 5.8 We believe that the much increased risk of morbidity and mortality for twins is the most important reason to reduce the number of multiple births, but we find that there are other reasons, too.

6. The health risks for mothers of twins

- 6.1 Multiple pregnancies and births significantly increase the health risks for mothers. A number of studies confirm that the general background risks of pregnancy and birth are much greater for women carrying twins. These include the risk of miscarriage, hypertension, anaemia, pre-eclampsia, glucose intolerance, haemorrhage, preterm labour and operative delivery.³⁵
- 6.2 Although the risk of maternal mortality (death) is still small, it is doubled for women expecting twins when compared to women who are pregnant with one baby, mostly due to the much increased risks of pre-eclampsia and haemorrhage. Up to 25% of multiple pregnancies are complicated by pregnancy induced hypertension, and the incidence of gestational diabetes is 2 – 3 times higher than in singleton pregnancies. The risk of pre-eclampsia increases almost 3-fold for twin pregnancies and is 9 times higher for women pregnant with triplets.³⁶
- 6.3 A recent population based study analysing all outcomes of multiple and singleton pregnancies in the Grampian region of Scotland confirmed the significantly increased risks for women carrying twins, ranging from fairly mild risks (for example threatened miscarriage) to serious, and potentially fatal risks such as haemorrhage or thromboembolism. The authors conclude that the instances of maternal and fetal morbidity that can be directly linked to IVF treatment are significant.³⁷
- 6.4 There are some women for whom a twin pregnancy is particularly dangerous. In these cases eSET is *medically* indicated: Congenital abnormalities of the uterus, bad obstetric history, previous loss of twins, previous severe prematurity in a singleton, cervical insufficiency, severe systemic disease (e.g. insulin-dependent diabetes, heart or respiratory disease).³⁸

7. Psychosocial consequences for families

- 7.1 Some mothers and families with twins experience severe parenting stress;³⁹ increased maternal depression, less possibility to work outside the home and an increased rate of divorce have all been reported for mothers of twins.⁴⁰ A recent review article of the available data on psychosocial outcomes for mothers of twins, particularly after fertility treatment, found that around 10% of mothers of twins experience depression, and that marital adjustment declined, particularly for first-time parents of twins.⁴¹ A Danish cohort study analysing health and social outcomes for all IVF children born in 1997 found that twins were a predictor of increased marital stress. First time mothers of low birthweight twins also reported that the birth of their children had a particularly high impact on their personal and social life.⁴²
- 7.2 There is also some evidence that parents who have twins after fertility treatments find looking after them even more stressful than parents of naturally conceived twins. Golombok *et al* found that mothers of IVF twins experienced significantly higher levels of stress than parents of naturally conceived twins. Significant differences were also found for fathers who reported that their interactions with their children were less rewarding, and the children themselves more difficult to deal with, than fathers of naturally conceived twins. There were no actual differences between the children's behaviour and the quality of the parenting, indicating that it is the IVF parents' perception that is different rather than the parenting.⁴³
- 7.3 A recent larger study, comparing parents of IVF twins and singletons, found again that there were no significant differences in child behaviour between the children (apart from cognitive development where twins showed significantly lower levels of development) but that parents of twins reported greater difficulties in parenting and more problems with child behaviour.⁴⁴ One possible explanation raised in the literature is that people's often lengthy and difficult experience of infertility and its treatment impacts on their experience of raising children, with parents possibly feeling less entitled to complain about being exhausted or overwhelmed, because they wanted children so much.⁴⁵ Also, more parents of IVF twins will be first time parents, a factor that has been identified as adding to parenting stress.⁴⁶
- 7.4 The risks of adverse psychosocial outcomes increase with each additional multiple birth child. A recent US study comparing mothers of IVF conceived singletons, twins and triplets found that for each additional multiple birth child, the odds of having difficulty in meeting basic material needs more than tripled, and the odds of lower quality of life and increased social stigma more than doubled. Each increase of multiplicity was also associated with increased risk of maternal depression.⁴⁷

8. Consequences for children's services

- 8.1 The increased health care needs of twins constitute a significant pressure on neonatal and paediatric services. A recent survey commissioned by the baby charity Bliss found that many neonatal units do not have sufficient staff and resources to care for the numbers of babies who need special, high dependency or intensive care. This may result in unsafe situations and over 70% of units have had to close their doors to admissions at times, as it would not be possible to receive any more sick newborns. It is especially difficult to find two cots in the same nursery for twins and also to find a bed for the mother. It is not unknown to have the mother in one hospital and each of the twins in two other hospitals. The shortfall in recommended nurse staffing levels was marked, with only three of the 143 units for which data were available achieving the required levels. The staff and cot shortages meant that many babies (at least three a day) were transported an average of 126 miles into different hospitals outside their own care network.⁴⁸
- 8.2 A number of studies attempt to assess the cost of care for often premature and low birthweight twins.⁴⁹ A recent study modelling the cost of care for IVF multiples in the NHS (up to 18 months) found that looking after a mother with twins was twice and with triplets four times as expensive as the care for a mother with a singleton pregnancy. The cost differential for looking after the babies themselves was even more striking: neonatal twin costs were 16 times higher than singleton costs; triplet costs 109 times higher.⁵⁰ Neonatal and paediatric services in the NHS, as well as social and special education services, are currently over-stretched, and the impact of rising twin numbers after IVF can only exacerbate an already difficult situation.⁵¹
- 8.3 We therefore believe that, while cost arguments should not by themselves determine healthcare choices, it is important that fertility service providers (who are often based in the private sector) take responsibility for the impact their working practices have on publicly funded services.

9. Summary: The nature and extent of the problem

- *There is overwhelming evidence that multiple pregnancies lead to much increased morbidity and mortality for mothers and children and can have negative consequences for parents and families.*
- *Given the above, as well as the resource intensive nature of many multiple pregnancies, we believe that multiple pregnancies after assisted conception must be reduced.*
- *It is now time that fertility centres consider the adverse impact of their work and act to reduce the number of twin births after IVF.*
- *To quote from Jan Gerris, a member of the expert group and one of the pioneers of single embryo transfer:*

'A positive pregnancy test is not a success; a healthy baby is. Two healthy babies at the same time are a success as well, but obstetricians know that it is difficult to predict which multiple will end well and which not. ... The problem is not any one particular twin [pregnancy] ending in the birth of two perfect children, but the epidemic size of the complications.' ⁵²

Possible Solutions

“You can have as many embryos back as you like, only one at a time.”

Dr Karl Nygren, Sweden, advice to IVF patients

The solution to the problem of multiple birth after IVF is seemingly simple: Women who are most likely to become pregnant with twins (these are the same women who have the best chance of becoming pregnant at all after IVF) need to have only one embryo transferred. However, if the solution was that straightforward, we are convinced the sector itself would have tackled the problem by now. The fact that this has not happened, points to the existence of obstacles that make progress in the desired direction more difficult.

The following section will explore eSET strategies and will analyse in some detail the difficulties that face those who attempt to reduce rates of multiple pregnancy after IVF treatment.

10. The principle for solving the problem

- 10.1 There are two principal ways in which the high number of multiple births after IVF can be lowered, one is elective single embryo transfer (eSET) for a large proportion of IVF patients, the other is selective abortion, also called multifetal pregnancy reduction, where one or more of the fetuses is aborted in order to achieve a singleton or lower order multiple birth.
- 10.2 We agree with the ESHRE Task Force on Ethics and Law that the prevention of multiple pregnancies through single embryo transfer 'should be preferred to multifetal pregnancy reduction (MFPR)'. The Task Force argued that MFPR was only 'morally acceptable if the physician had acted according to the rules of good clinical practice and had tried to minimise the risk of a multiple pregnancy.'⁵³ Between 2002 and 2005, 27 fetal reductions were reported to the HFEA by fertility clinics. However, the figures that are reported are likely to give an incomplete picture, since clinics might be unaware of women undergoing fetal reductions. The Department of Health collects data from abortion services themselves. Their figures for fetal reductions are higher: In 2004, 64 cases of fetal reduction were reported, about half of these were performed on twin pregnancies. It is very likely that the fetal reductions performed on twin pregnancies were undertaken because of severe fetal abnormality, since it is not usual for a twin pregnancy to be reduced to one. The figure for 2003 and 2002 is 65.⁵⁴ The latest European dataset shows that there were 461 reported fetal reductions in Europe in 2002 (not all countries would have systems of recording these systematically). Without this technique the number of triplet births would probably have been higher, considering that the number of reported reductions is almost as high as the number of recorded triplet deliveries.⁵⁵
- 10.3 Without repeating all the moral arguments about abortion, it is obvious to our group that eSET is the preferable option for lowering the number of iatrogenic (medically induced) multiple births.⁵⁶
- 10.4 The solution for reducing the number of multiple pregnancies is therefore clear:
- IVF patients with a relatively good chance of pregnancy need only have one, rather than two embryos transferred;
 - Their chance will be influenced by factors such as age, medical and treatment history, and the quality of the embryos used for treatment;
 - It might not always be easy to decide who these women are – but women who have non-identical twins after two embryo transfer would in all likelihood have also become pregnant if a single embryo had been transferred.

10.5 Despite there being a seemingly simple solution to the problem of iatrogenic twins - elective single embryo transfer (eSET) ⁵⁷ - we have identified a number of factors that will make progress difficult.

They are:

- The need to maintain acceptable pregnancy rates for patients with different prospects of success;
- The lack of NHS funding for IVF and the failure (so far) to implement the NICE guideline on fertility treatments consistently;
- Patient and clinician views on eSET;
- HFEA data collection and reporting of outcome data;
- The nature of the UK fertility sector, with the majority of treatments taking place in the private sector.

10.6 The following sections of this paper will discuss the difficulties any policies on reducing multiple births will have to tackle, before listing our recommendations.

11. Maintaining live birth rates

11.1 Selecting the appropriate sub-group of patients for eSET

11.1.1 The objective to minimise multiple pregnancies needs to be balanced with the need to maintain acceptable birth rates for IVF. Only ever putting back one embryo, regardless of the woman's prognosis would virtually eliminate multiple births after IVF, but would also lead to a marked reduction in pregnancy rates for many fertility patients.⁵⁸ Therefore we do not suggest that all women under all circumstances should only ever have one embryo put back as part of their IVF treatment.

11.1.2 Existing HFEA Register data on single embryo transfer cycles cannot be used to assess birth rates after eSET, since currently the vast majority of cycles where only one embryo was transferred will not have been elective, i.e. only one embryo was transferred because it was the only embryo available.⁵⁹ The expert group therefore reviewed the available international data.

11.2 Randomised controlled trials

11.2.1 A number of randomised controlled trials confirm that the pregnancy rates are still higher after two embryos are transferred (double embryo transfer, DET) than after eSET in the first fresh cycle, even for a selected group of patients (those with relatively good prognosis). The discrepancy is reduced or eliminated when pregnancies following a subsequent frozen/ thawed transfer cycle are added, when some trials have found no significant⁶⁰ differences for pregnancy rates between eSET and DET.⁶¹

- In 1999 Gerris *et al* performed eSET in women under 34 who started their first IVF/ICSI cycle and had at least 2 good quality embryos.⁶² The study showed that the ongoing pregnancy rate was higher in the double embryo transfer group than in the single embryo transfer group (74.1% versus 38.5%). However, the ongoing pregnancy rate in the eSET group was still equal to or higher than the generally accepted monthly conception rate of couples with normal fertility. The twin rate in the DET group was around 30%, in the eSET group only one woman gave birth to (monozygotic) twins.

- Martikainen *et al* conducted a randomised controlled study (between eSET and DET) on women of all ages who had at least 4 good quality embryos and no more than one failed treatment cycle. The treatment outcomes including those after frozen embryo transfer were compared between the two groups. The clinical pregnancy rate per transfer was 32.4% in the eSET group and 47.1% in the DET, the difference being not significant in statistical terms.⁶³ The cumulative clinical pregnancy rate after transfer of both fresh and frozen embryos was 47.3% in the one embryo transfer group and 58% in the two embryo transfer group. The twin rate was 39% for the DET group, there was only one pair of monozygotic twins in the eSET group.⁶⁴

- Thurin A *et al* from Sweden conducted a randomised multi-centre study comparing eSET plus frozen/thawed cycle with DET in 661 patients less than 36 years old who had at least two good quality embryos. The pregnancy rate resulting in at least one live birth was 38.8% in the eSET plus frozen ET group and 42.9% in the DET group. The twin rate was 0.8% and 33.1%

respectively. The study showed that eSET, plus eventual frozen embryo transfer, led to a dramatic reduction of the multiple births rate without a substantial reduction in the overall rate of pregnancy.⁶⁵

- In 2005 Lukassen *et al* attempted to assess the cost effectiveness of two eSET cycles versus one DET cycle on the basis of a study sample of 108 Dutch women.⁶⁶ They found that two fresh cycles of eSET were equally effective as one DET (41% versus 36% ongoing pregnancy rate), but that there were no twin pregnancies in the eSET versus 37% twin pregnancies in the DET arm of the trial. Taking into account the higher costs of caring for premature and low birth weight twins, the medical costs per live birth up to 6 weeks after delivery were the same for both groups. However, when lifetime costs for severe handicap were included in the modelling, more than €7000 were saved per live birth after eSET.⁶⁷

- In 2006 Thurin *et al* investigated the obstetric and paediatric outcomes and the cost effects in their earlier study group (see above). They found that there were markedly more maternal and paediatric complications in the DET than in the SET group (for example: severe neonatal complications: 33.9% versus 17.8%; 24.3% of children had two or more complications, versus 7.8%). They concluded that the eSET strategy was superior to the DET strategy, when number of deliveries with at least one live-born child, incremental cost effectiveness ratio and maternal and paediatric complications were taken into consideration.⁶⁸

11.2.2 There were also two reviews of the then existing randomised controlled trials on eSET versus DET in 2005. Christina Bergh⁶⁹ reviewed the existing RCTs (above) and concluded that in good prognosis patients satisfactory delivery rates can be achieved with eSET. The delivery rate was significantly lower after eSET, but was restored with the addition of frozen-thawed embryo transfers.⁷⁰

11.2.3 Finally, a Cochrane review of the available randomised controlled trials concluded that eSET significantly reduces the risk of multiple pregnancy, but also decreases the chance of live birth in a fresh IVF cycle. Subsequent replacement of a single frozen embryo achieves a live birth rate comparable with double embryo transfer.⁷¹

11.2.4 The various trials have slightly different inclusion criteria for the eSET group. All the studies perform eSET in good prognosis patients.⁷² The prognosis is based on various combinations of a number of factors:

- Age of the woman⁷³;
- Number of previous failed IVF attempts;
- Basal FSH level / ovarian response;
- Number and quality of embryos available⁷⁴.

11.3 Observational studies and national data sets

11.3.1 Various groups also conducted a number of observational or cohort studies on success and multiple rates after eSET vs. DET. The difference between observational studies and randomised clinical trials was that the patients whose outcomes were compared had not been allocated randomly to their respective treatment arms and hence selection bias, temporal differences and population variation could influence the results obtained. Once the policy change to eSET was introduced in Sweden, Finland and Belgium, clearly, randomisation could no longer take place because certain given groups of women were required to be treated with eSET rather than DET. The observational studies, however, can give a more accurate picture for what happens when eSET policies for a certain sub-group of patients are introduced nationally. The existing observational studies have recently been reviewed and summarised by two authors: Bergh (2005) and Gerris (2005). Bergh concluded that the pregnancy rates were the same in eSET and DET groups. ‘The reason for achieving similar results is of course that the two groups are not strictly comparable; good prognosis women receive eSET while poor prognosis women receive DET.’⁷⁵

11.3.2 Gerris summarises the outcomes of the various trials in the table below (*Human Reproduction* 2005; 20: 325).⁷⁶

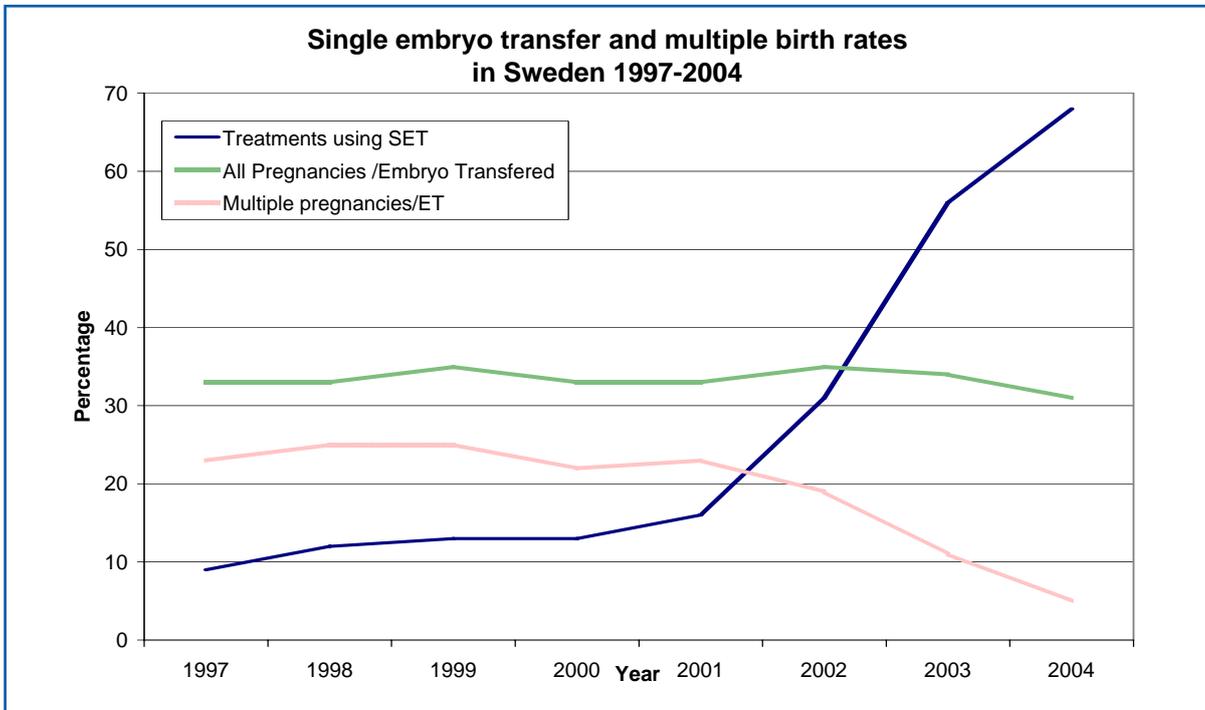
Randomized studies and cohort studies comparing single with double embryo transfer					
Study	No. of cycles	Single embryo transfer		Double embryo transfer	
		Pregnancy rate (%)	Twins (%)	Pregnancy rate (%)	Twins (%)
Randomized trials					
Gerris <i>et al.</i> (1999)	53	10/26 (38.5)	1/10	20/27 (74)	6/20 (30.0)
Martikainen <i>et al.</i> (2001)	144	24/74 (32.4)	1/24	33/70 (47.1)	6/33 (18.2)
ardner <i>et al.</i> (2004)	48	14/23 (60.9)	0/14	19/25 (76)	9/19 (47.4)
Thurin <i>et al.</i> (2004)	661	91/330 (27.6)	1/91	144/331 (43.5)	52/144 (36.1)
	+ cryo	131/330 (39.7)	1/131		
Total	906	139/453 (30.7)	3/139 (2.16)	216/453 (47.6)	73/216 (33.8)
Cohort studies					
Gerris <i>et al.</i> (2002)	1152	105/299 (35.1)	1/124	309/853 (36.2)	105 + 5/309 (35.6)
De Sutter <i>et al.</i> (2003)	2898	163/579 (28.2)	1/163	734/2319 (31.7)	219 + 4/734 (30.4)
Tiitinen <i>et al.</i> (2003)	1494	162/470 (34.5)	2/162	376/1024 (36.7)	113/376 (30.1)
Catt <i>et al.</i> (2003)	385	49/111 (44.1)	1/49	161/274 (58.8)	71/161 (44.1)
Gerris <i>et al.</i> (2004)	367	83/206 (40.3)	0	65/161 (40.4)	20/65 (30.8)
Martikainen <i>et al.</i> (2004)	1111	107/308 (34.7)	1/107	255/803 (31.8)	NA
		187/308 (60.7)			
Total	7407	669/1973 (33.9)	6/591 (1.0)	1900/5434 (35.0)	537/1645 (32.6)

Data for the Martikainen (2001) study and the Thurin (2004) study show both the fresh and the cryo-augmented pregnancy rates.
HOMP = high order multiple pregnancies; NA = not applicable.

1.3.3 According to Gerris, the studies illustrate two main points. Firstly, cryopreservation is an important tool for maintaining success rates after eSET. Secondly, transferring the ‘two best’ embryos always yields more pregnancies than transferring only ‘the best embryo’. ‘There is no point in saying that eSET equals DET. This is clearly shown when comparing the results after eSET versus DET between the randomised and the cohort studies.’ He points out that good eSET policies balance the desire for high pregnancy rates with the need for patient safety (and improved health outcomes for children).

11.3.4 Karl Nygren, one of the members of our group, presented some relevant data about the correlation between eSET and multiple rates in Sweden.

Correlation between eSET rates and multiple rates



11.3.5 Two things can be gleaned from this graph: firstly, looking at the year-on-year development of the eSET and the pregnancy rates, the overall pregnancy rate remains the same over the years. Thus, in Sweden, the introduction of eSET policies did not seem to reduce women’s chances to conceive. Secondly, there is a clear correlation between the eSET rate and the multiple pregnancy rate:

- Doing 30% eSET cycles leads to a twin birth rate of around 20%;
- Doing 50% eSET cycles leads to a twin birth rate of around 10%;
- Doing 70% eSET cycles leads to a twin birth rate of around 5%.

11.3.6 This correlation has also been confirmed by other international data sets, such as the Danish and Finnish experience (Karl Nygren, Chair of European IVF Monitoring, oral presentation at the expert group meeting on 22 December 2005).

11.4 Maintaining pregnancy rates – a real life perspective

11.4.1 Some of the patients’ views we reviewed made it clear that ‘maintaining pregnancy rates’ may be viewed differently by patients and clinicians. The academics whose work we reviewed (above) often conclude their papers by stating that eSET leads to success rates similar to natural conception (which is estimated to lie somewhere between 20 and 25 % per cycle). Also, many clinicians agree that pregnancy rates should be viewed *cumulatively*, i.e. all the (quality) embryos

created after one egg collection should be used one after the other, and success rates only calculated at the end of the process, when all the embryos arising from one egg collection have been used.

- 11.4.2 However, things are not that straightforward when viewing the IVF process from the patient perspective.⁷⁷ Needing additional thawed embryo transfers will cost many patients more money, but it will also mean more time off work, more trips to hospital, more invasive treatment, more consultations, more medication, and crucially, more hopes being raised and then crushed as cycles fail. It also seems to us that the comparison of IVF pregnancy rates to natural conception rates is not appropriate. Having three failed IVF cycles cannot be compared to trying to conceive for three months by having sex with a partner. Some patients compare failed IVF cycles to early miscarriages, so going through three failed attempts of IVF might be more like having three miscarriages. And no-one would deny that this would be distressing or even traumatic.
- 11.4.3 We feel that an important part of any argument about cumulative or fresh/frozen pregnancy rates is to acknowledge that IVF is an often distressing, invasive and painful process. In particular, there should be a recognition of the extra stress and discomfort that can result from patients needing an additional treatment cycle in order to become pregnant. Patients will not be convinced of the need for change if it is not clear that we have considered the difficult reality of undergoing fertility treatment.

11.5 Embryo selection

- 11.5.1 In order to maintain pregnancy rates with eSET it is important to be able to choose the embryo with the highest chance of implantation for the initial transfer. Embryo selection is also a crucial part of a successful embryo freezing programme. Embryo grading systems are not uniform across the UK, let alone internationally. One could argue that it does not matter whether two clinics judge embryos differently, as long as they have good data and experience to be able to predict whether *in their clinic, with a given patient*, a given embryo has a good chance of implantation. This ability to predict implantation rates can be based on good clinical audit – and the lack of agreement between clinics is not a problem *per se*; it is possible that embryo handling and patient characteristics might vary between clinics and that embryos might indeed have different implantation potential. However, the argument has also been made that more uniform and transferable grading systems would help assure quality between clinics, and would help to identify the differences in laboratory techniques.
- 11.5.2 An early multi-centre pilot external quality assurance scheme run on behalf of the Association of Clinical Embryologists (ACE) demonstrated marked differences in morphological assessment even when provided with the same image of a cleavage stage embryo. It is also clear that very varied criteria are applied to embryo freezing, with some clinics freezing many more embryos than others, which indicates that a variable proportion of embryos is deemed suitable for freezing. ACE is planning a revised grading scheme on DVD with movie clips of embryos, which will be closer to a real embryo evaluation. It is hoped that this will promote internal evaluation of variations in grading, as well as comparison between laboratories. It might also promote discussion about embryo selection and support the development of a nationally agreed embryo grading and assessment scheme.

11.5.3 To this end, the revised ACE scheme uses a grading system that, it is hoped, will be acceptable to UK clinics. The scheme is based on three broad factors:

- Number of blastomeres;
- Evenness of cell division;
- Degree of fragmentation.

11.5.4 We have also been informed of the work of a group of Swedish scientists who have developed a computer-based embryo scoring (and a treatment prediction) model. They found that blastomere number, blastomere size variation and the presence of mononuclearity in the blastomere were the most decisive factors determining implantation rates. The embryo scoring model was also combined with a clinical prediction model (taking into account numerous clinical factors) in order to minimise twin implantation while maintaining high pregnancy rates. Analysing 80 variables, it found that only four were significant and independently predictive of implantation rates: embryo score, age of the woman, ovarian sensitivity (number of eggs retrieved in relation to total number of FSH units administered) and number of previous IVF attempts, taking into account previous IVF pregnancy or not.⁷⁸ It seems to us that this work is highly relevant to UK attempts to develop more consistent embryo selection and eSET criteria.⁷⁹

eSET and blastocyst transfer

Good success rates have been reported for transfers on day 5, rather than day 3.⁸⁰ However, the studies that report higher success rates also demonstrate that the multiple birth rates are even higher where two blastocysts rather than two cleavage stage embryos are transferred. Only better quality embryos will survive for 5 days in culture and form blastocysts, so it is not surprising that they have higher implantation rates, leading to higher multiple rates. A Cochrane review of the best available evidence found no significant differences in success rates, but identified the multiple rate as one of the 'secondary advantages or disadvantages' that should be addressed through further research.⁸¹

Gardner et al. (2004) reported the outcomes of a small American randomised trial comparing single and double blastocyst transfers in 48 women. Single blastocyst transfer maintained very high pregnancy rates (60.9%) with no twins, compared to 76% pregnancy rates after double blastocyst transfer, with a twinning rate of 47.4%.

A recent observational study reviewing outcomes after single or two blastocyst transfer confirmed the striking twin rate after double blastocyst transfer (Criniti et al 2005),⁸² with 62% twin pregnancies (as compared to 3.2% after single blastocyst transfer). Henman et al (2005) left it to the patients to decide whether to transfer one or two blastocysts. 121 women chose single blastocyst transfer, 285 chose to transfer two. After a fresh and one frozen cycle, virtually identical pregnancy rates were achieved (65.3% after single transfers vs. 64.2% after double transfers), but there were only 7% twin pregnancies in the single transfer group, compared to 34% after 2 embryo transfer. The increased risk of twin pregnancy led to 5 perinatal deaths in the double blastocyst transfer group.⁸³

In our view, eSET is clearly the way forward for patients who have embryos good enough for blastocyst culture and more than one good blastocyst on day 5 or 6.

11.5.5 Our group is aware that it is not possible to base HFEA guidance to clinics on embryo grading criteria because it is impossible to reconstruct and check embryo quality once embryos have been transferred. However, we believe that moves to develop more consistent embryo grading schemes would be welcomed since clinics themselves will have to develop reliable and quality assured systems of embryo selection once the move to eSET is made.

11.6 Summary: Maintaining pregnancy rates

The expert group reviewed a wide range of international data comparing pregnancy rates after eSET and DET:

- *Although controlled trials tend to show lower pregnancy rates following one fresh cycle after eSET than DET, international data sets which include much larger numbers of cycles, do not confirm that trend: Where eSET has been introduced as the norm, pregnancy rates have not dropped, but multiple birth rates were reduced significantly.*
- *Selection criteria for both patients and embryos enable clinics to balance the need to reduce the number of multiple births with the desire to maintain acceptable pregnancy rates.*
- *Fresh cycles should be followed by frozen thawed embryo transfers based on good cryopreservation protocols in order to achieve equivalent pregnancy rates without the risk of multiple pregnancy.*
- *It is important to acknowledge that – although cumulative pregnancy rates might remain high – extra treatment cycles place a burden on patients. NHS funding for extra cycles and cryopreservation would at least ensure that patients are not also left with additional financial costs.*
- *Where there is more than one good blastocyst on day 5/6, we believe the case for single blastocyst transfer is overwhelming.*

12. NHS commissioning for IVF and the variation in implementation of the NICE guideline

- 12.1 In 2004, NICE, the National Institute for Clinical Excellence published its clinical guideline on fertility treatments. This guideline recommended that the National Health Service (NHS) in England should provide three cycles of IVF/ICSI to couples where the woman is aged between 23 and 39 and who have an identified cause of their fertility problems or unexplained infertility of at least three years duration. In an accompanying statement (the first of its kind for any clinical guideline), the then Secretary of State for Health, Dr Reid, stated that every Primary Care Trust (PCT) should provide eligible couples with at least one NHS funded cycle of treatment from April 2005, with full implementation (three cycles including frozen/thawed follow-on cycles) expected to be offered 'in the long term'. Aware of the significant investment required for full implementation, he went on to advise PCTs that in the first instance, priority should be given to people without children living with them. The situation is different in Scotland and Northern Ireland, where NICE guidelines do not apply, but there too, fertility services are rationed.⁸⁴
- 12.2 The expert group discussed a survey conducted by the All Party Parliamentary Group on Infertility, in partnership with the National Infertility Awareness Campaign (NIAC) in March 2005 immediately prior to the deadline for implementation of the NICE guidance. 186 responses were received representing the position of 214 PCTs (many PCTs commission in consortia), a response rate of 71%. The results indicated that the NICE guideline was unlikely to be implemented consistently. When asked to comment on the steps they were taking to ensure that they met the April 2005 requirement to fund at least one full cycle, 58% planned to have this provision in place to meet the deadline, however, 16% reported that they were still assessing the steps needed to comply or did not comment on progress, hence it is unclear what level of provision is available in those areas. Progress could also not be assessed amongst the 29% of non responding PCTs. 179 (83%) PCTs funded IVF at that time and data was available on the number of cycles funded per couple in 159 (89%) of the responses. Variation was apparent between PCTs, 70 (44%) funded 1 cycle of IVF compared to 66 (42%) funding 2 cycles and 23 (14%) funding 3 cycles. Of concern was the finding that 20 PCTs reported their intention to reduce current provision, with 11 planning a reduction from 2 cycles to 1 and a further 9 organisations from 3 cycles to 1. This option was stated to be unacceptable by a Minister of Health in response to a parliamentary question and the current provision of those PCTs is unknown. However, this approach indicates a clear reluctance on the part of some commissioners to ascribe a higher priority to fertility services. Since this survey was performed, some PCTs, whose original response indicated funding one cycle of IVF, have announced that they have ceased funding IVF treatment as part of a financial recovery plan with a resumption of funding to be considered in 2007.⁸⁵
- 12.3 It should be noted that across the UK provision of IVF services shows a geographic variation with lowest levels of provision being apparent in the south and highest provision in Scotland. In addition, some PCTs, notably those in the North West, i.e. Cheshire & Merseyside, Greater

Manchester, Cumbria and Lancashire, have consulted widely and worked diligently in order to both continue to offer current levels of treatment (2 cycles) as well as planning for full implementation.

12.4 The NIAC survey also confirms that in implementing NICE guidance, the clinical eligibility criteria contained in the guideline have been accompanied by other criteria. These reflect the local priority NHS commissioners have given to fertility treatments relative to the other health needs of their population.

In general they restrict access to treatment based on:

- The effectiveness of treatments in specific groups, for example restricted provision of treatment for
 - smokers;
 - women outside a BMI range of 19-30;
 - those who have had previous failed cycles of IVF/ICSI whether self or NHS funded;
- The Secretary of State's instruction to prioritise funding for those who did not have children living with them (in some areas this has been interpreted as a requirement that one or both partners are completely childless);
- Other policies (for example no NHS funding for reversal of sterilisation or subsequent fertility treatment, except in exceptional circumstances);
- Methods of demand management (for example in Thames Valley and Hampshire, only women over the age of 34 can join a waiting list for IVF).

The group agrees with its panel member and Infertility Network UK (INUK) Chief Executive, Clare Brown, that in many cases 'this situation is neither cost nor clinically effective'.⁸⁶

12.5 The group also discussed a survey conducted by the HFEA amongst its 'Patient Panel'.⁸⁷ This survey of more than 500 patients confirmed that access to funding is the biggest obstacle to patient acceptance of eSET policies. Three quarters of respondents who initially opposed eSET stated that they would be more likely to consider having one embryo transferred, if NHS funding was routinely available for 3 cycles of treatment.

12.6 The group is aware that those health systems that have successfully moved to routine eSET policies and have therefore significantly reduced their multiple birth rate have done so in the context of publicly funded fertility services for at least three IVF cycles.⁸⁸ The group agrees unanimously that the lack of publicly funded fertility treatments is the most significant obstacle to an acceptance of changing embryo transfer practices towards a reduction in the twin rate in the UK. Patients who have to find funding for their treatments themselves or who only have access to one NHS funded attempt (often after a lengthy wait) will be more resistant to even the smallest decrease in success rates than patients who know that they can have three funded attempts at starting a family. Similarly, clinics which compete for private patients - who necessarily focus all their hopes and expectations on one fresh IVF cycle - will be more reluctant to risk an even small drop in success rates. We are therefore convinced that better NHS funding of IVF, i.e. full implementation of the NICE guideline, would enable the sector to make progress much more easily than the current inconsistent funding situation.

- 12.7 We are particularly concerned that NIAC and INUK have discovered that not all PCTs include the freezing of additional embryos in their funding for one IVF cycle. In order to make progress towards eSET policies, the availability of freezing programmes based on good protocols is of central importance. It strikes us as not only clinically, but also ethically questionable to resource the creation of embryos, but then not to fund their storage and later use. The Department of Health statement accompanying the launch of the NICE clinical guidance contained the specification that for the purposes of NHS funding, an IVF cycle should include frozen embryo replacement. The group strongly urges the Department to repeat this statement and audit its implementation as a matter of urgency.
- 12.8 Some of our members argued that there should be a clear link between any policy change on multiple births and implementation of the NICE guideline. In their view, patients would be unacceptably disadvantaged if eSET policies were introduced without progress on funding issues. They stressed that the extra funding required for better access to IVF treatments would be more than compensated for by anticipated savings in neonatal, paediatric and subsequently, education and social services. However, other members of the group were less optimistic that the Department of Health and the NHS, with its various fund-holders, commissioners and budget constraints, can be convinced of this sensible long-view approach, and believe that the HFEA and the fertility sector are obliged to address the problem of multiple births as a matter of good clinical practice despite the erratic and unsatisfactory funding situation.

12.9 Summary: Reducing multiple births and improving access to NHS funded treatments

- *We are in complete agreement that the failure to implement the NICE guideline on fertility (3 cycles of IVF for all eligible patients) is the major obstacle to the acceptance by patients and clinicians of introducing eSET policies in the UK.*
- *Implementing the NICE guideline and introducing eSET policies would solve two problems at the same time. Namely a reduction in the current unacceptable level of iatrogenic multiple births and sustaining birth rates that are acceptable to both patients and clinicians alike. The group is convinced that the marginal increase in costs by including freezing, and the additional cycles, would be offset by the financial savings expected were there fewer iatrogenic multiple births.*
- *Some members of the group would be reluctant to see eSET policies introduced without full implementation of the NICE guideline. Others believe that the necessary improvements to clinical practice in the fertility sector should not be held back by the potentially intractable nature of NHS funding issues.*
- *Whilst recognising the importance of local prioritisation in matching health services to the resources available, experience both internationally and from countries within the UK demonstrates that a national approach is not only feasible but desirable. We are of the opinion that a statement by the Department of Health on the place of fertility treatment within the overall prioritisation of health services, followed by a robust audit of implementation of that guidance would result in a significant improvement of access.*

13. Patient views

13.1 There were patient representatives on the expert group and we also discussed the academic literature and other data on patient views.

- In 2003 a Danish team of researchers (Pinborg *et al*) interviewed women who had 3 to 4 year old twins after IVF, mothers of naturally conceived twins and mothers of IVF singleton babies (1769 women in total) about their views on eSET.⁸⁹ Many mothers of twins were still not convinced of the need for eSET and actually preferred twins. However, the study found that having had a child with very low birth-weight was highly predictive of an acceptance of eSET, highlighting the fact that only parents who have experienced the stress of twins who were unwell at birth take the risk of multiple births seriously enough to accept eSET.
- A group of academics in the UK assessed the effects of various ways of providing information about the risks of twins on couples' perception of eSET (Murray *et al* 2004).⁹⁰ The study found that additional information and counselling did not significantly change the couples' views on eSET, but that a fixed charge for all fresh and frozen embryo transfers following a single oocyte retrieval would lead to significantly increased acceptance of eSET policies. The perceived pregnancy rate after DET or eSET was the other determining factor for couples' attitudes.⁹¹
- A Swedish study in 2005 (Blennborn *et al*) investigated the factors influencing the decision to have eSET or DET amongst 274 IVF patients.⁹² It found that the patients had a good knowledge of the risks of multiple pregnancy. Around 60% of couples chose DET, 40% eSET. The study found that younger age and shorter duration of infertility, but most importantly the experience of previous childbirth and the availability of spare embryos to freeze were factors leading couples to choose eSET, whereas perceptions of higher success rate and previous IVF attempts were factors indicating a preference for DET.
- A smaller study comparing clinicians', embryologists' and patients' views on embryo transfers, multiple pregnancies and blastocyst culture (Hartshorne and Lilford 2002) found that patients were willing to take greater risks of multiple pregnancy after blastocyst transfer than the professionals involved deemed appropriate.⁹³

- 13.2 The group also discussed the views generated by the HFEA's Patient Panel and an online discussion held on the Fertility Friends website.⁹⁴ The Patient Panel generated the following responses:
- Most participants (72%) said they were given information about the risks to mothers and babies resulting from multiple embryo transfer, but only a minority (9%) changed their attitude towards multiple embryo transfer because of this information;
 - Over half (57%) would not agree to having one embryo transferred in order to minimise the chance of a multiple pregnancy, even if medical staff felt it was appropriate for them;
 - However, three quarters (75%) of these people would be more likely to consider having one embryo transferred if NHS funding was routinely available for 3 cycles of treatment.
- 13.3 The majority of respondents to the Fertility Friends discussion argued that the HFEA should be producing recommendations or guidelines rather than firm regulations, and highlighted the importance of judging each patient on a case by case basis. It was also apparent from some of the mailings that patients were not receiving good information about the risks of multiples and that, whether they had received this information or not, it was generally felt that twins were a positive outcome. A significant number of patients argued they would be more inclined to accept eSET if they received funding for a number of cycles.
- 13.4 All these sources of information show that many patients are resistant to the idea of eSET, mostly because they fear that their chances of getting pregnant will be reduced. It is also evident that questions of funding are central to patients' attitudes about eSET. We are aware that convincing patients of the need for a policy change is going to be difficult, especially in the context of unsatisfactory levels of NHS funding for infertility treatment in most parts of the UK.
- 13.5 We also discussed the possibility that patients who feel strongly that their chances of pregnancy would be compromised by eSET policies might go abroad to receive treatment with as many embryos as they wish. There are other areas of HFEA policy that have led to patients going abroad who don't accept the treatment choices in the UK (sex selection and anonymous sperm donation). Despite this so-called 'reproductive tourism'⁹⁵, patients seeking multiple embryo transfers abroad would probably still come back to the UK to have their babies, which would still impact on NHS neonatal and children's services. Patients cannot be prevented from travelling to where they perceive the best treatment to be⁹⁶, but this does not detract from the HFEA's responsibility to issue the guidance that has been identified as best for UK practice. Also, we are convinced that the majority of patients would prefer to stay in the UK rather than travel abroad for their fertility treatment. Thus the impact of changed HFEA policy and clinical practice on multiple birth rates should still be significant. We also hope that, once the current unequal and inconsistent funding situation improves, fewer patients would feel compelled to go abroad.
- 13.6 The differences in international experience also highlight how central to patients' decision making clinicians' views and advice are. International colleagues tell us that once the transition has been made, patients accept the reasons for, and benefits of eSET. The group therefore feels that changing patients' attitude to eSET will not be possible if clinicians themselves (including embryologists, nurses, counsellors and so on) are themselves not convinced nor convincing.

13.7 The frequency of seeing healthy twins makes it difficult for patients to comprehend the adverse risks of multiple pregnancy. The press and television seldom highlight the downsides of multiple pregnancy, often sensationalising higher order pregnancies. Patients with twin or triplet pregnancies are often reluctant to be filmed as matters unfold adversely, and clinics tend not to want to be associated. The data suggests that sadly it is often only direct experience that can sway patients' opinions. In the absence of that, we believe it is the clinician's professional responsibility to increase their own knowledge about the risks and to communicate it effectively to the patients in their care. Unfortunately, some clinicians do not themselves recognise that multiple pregnancy carries a significant risk. The HFEA, the professional bodies and patient groups all have a role to play in improving the information given on multiple birth risks and to convey a sense of urgency about the issue.

13.8 Summary on patient views

- *The expert group is aware that many patients are resistant to the introduction of eSET policies because they fear their chances of getting pregnant will be reduced especially in circumstances in which they have access to only one NHS treatment cycle (if they can access NHS funding at all).*
- *Improving access to NHS funded treatment would increase patient acceptance of eSET.*
- *The fertility sector (clinics, HFEA, professional bodies, patient groups), as well as other organisations, such as the Multiple Births Foundation, play a vital role in explaining the risks and frequency of multiple births in order to facilitate the required change in attitude.*
- *Clinicians, nurses and counsellors have the most important role to play in helping their patients understand the real nature of these risks.*

14. HFEA data collection and reporting

- 14.1 Section 8 of the HFE Act 1990 obliges the HFEA to provide information about licensed centres and activities. The HFEA has always understood this obligation to include (amongst other things) the publication of outcome data, based on the ongoing data reporting from clinics to the HFEA. Currently, the HFEA publishes live birth rates for each licensed clinic, expressed as live birth per cycle started. As outlined above, the birth rates per single fresh cycle might appear lower after eSET than DET, unless frozen thawed cycles are included and outcome statistics are cumulative per cycle of stimulation.
- 14.2 We heard evidence from clinicians who argued that this approach to publishing outcome data was an important obstacle to changing clinical practice towards eSET. Clinics which are competing for patients are concerned about success rates and will avoid any move that risks their place in the 'league table'. We are aware that the HFEA does not itself compile or publish league tables and that it also provides further information to help patients interpret the data. The publication of birth rates per cycle started without the inclusion of freeze thaw cycles, however, will favour clinics that perform more DET although they will show significantly higher multiple rates.
- 14.3 The group heard from HFEA register staff and from external experts that provision of information per egg collection or even per woman treated would be difficult under the current data collection system: individual forms are filled in per cycle, not per woman and data is returned in yearly cycles making it difficult to accumulate birth rates based on one egg collection. Sometimes frozen embryos from different treatment cycles are also pooled for an embryo transfer, rendering linking frozen and fresh cycles even more difficult.
- 14.4 We also discussed other ways of making the risks of multiples more obvious in the HFEA data reporting. One suggestion was to subtract all multiple births from the published birth rates and therefore to define a successful outcome as only the birth of a singleton baby. However, the group felt that as a public body it would be inappropriate for the HFEA to 'withhold' information it had collected about clinical practice, and it was obliged to publish all the available data, multiple births included. Other suggestions included star-rating or even black-marking of clinics according to how well (or badly) they manage to reduce their multiple birth rates. If the HFEA decided to explore this possibility further, it should formally involve clinics and patients in developing the rules for the ranking process.
- 14.5 However, we also believe that too much can be made of the significance of outcome reporting. If HFEA policy was changed and all clinics had to work to new guidelines, there would be a level playing field again as happened when the change from three to two embryo transfer was made. With a year's time lag, all clinics report their data on the basis of changed clinical practice.
- 14.6 Clinics are also obliged to take into account the welfare of the child or children born after IVF (section 13 (5) HFEA Act). The significantly increased risks of morbidity and mortality resulting from multiple births are currently the biggest known threat to ART children's welfare. Clinical practice needs to change in order to take account of this by giving ART children the best chance to be born undamaged and at full-term. Pursuing higher success rates should not get in the way of looking after the best interest of IVF children.

- 14.7 The HFEA publishes patient information, in the form of fact sheets on individual subjects, the annual patient guide, and the HFEA website. In recent years, much effort has gone into improving this information and many patients have expressed how valuable HFEA patient information has become to them. However, there is little information about multiple births available in HFEA publications, and we believe that this information needs to be strengthened significantly in order to support any change to policy.
- 14.8 We also discussed the desirability of linking HFEA register data to wider outcome data in order to assess the health of children born after IVF. If this linkage were possible, the levels of morbidity amongst children born as a result of an IVF multiple pregnancy could be determined. More precise assessments could be made of the resources the NHS has to commit to looking after multiple births infants resulting from IVF and how many multiple birth infants from any particular clinic required additional or long-term care. Currently, none of this is possible because of confidentiality restrictions originating from the 1990 legislation (section 33 HFE Act). We hope that the ongoing review of the 1990 Act will rectify this unsatisfactory situation. Since the number of ART children is steadily rising (in some countries, 4% of all births are now following ART), research into the health outcomes of these children is becoming increasingly important.

14.9 Summary: HFEA information

- *The publication of birth rates per cycle started, and their adaptation into 'league tables' of success by fresh cycle outcome alone, does not encourage clinicians and patients to change their views on multiple births.*
- *The HFEA should explore ways of emphasising the desirability of singleton births in its patient information and its publication of outcome data.*
- *The group does not believe that withholding information is feasible, but hopes that ways can be found to provide information about singleton and multiple birth rates that enable patients and clinics to assess performance in a balanced way.*
- *The group feels that information about the risks and possible complications of multiple births provided by the HFEA to patients needs to be strengthened considerably.*

15. The nature of the UK fertility sector

- 15.1 Much of the data we reviewed was collected outside the UK, with some of the Nordic countries (Sweden, Finland and Denmark) and Belgium leading the way towards lower multiple birth rates after IVF. We therefore discussed to what extent this data is transferable to the British fertility sector.
- 15.2 It is possible that in the UK, because of the lack of publicly funded IVF and long waiting times, patients might be slightly older, or have more intractable fertility problems than abroad, where it is easier for patients to be treated by fertility specialists. The fact that most provision of fertility services in the UK is in the private sector might also affect clinical practice and the impact that eSET policies could have in the UK. For example, patients are usually charged extra for freezing spare embryos and subsequent thaw transfer cycles, which might reduce their support for eSET. We also heard anecdotal evidence that clinics use various and different protocols for freezing embryos, which makes it hard to compare survival rates for embryos after freezing and thawing. Profit margins may skew clinics offering fresh vs. frozen cycles. Some clinics might freeze only top quality embryos, whereas others would freeze lesser quality embryos too. We are also concerned that clinics across the sector do not necessarily have consistent embryo rating and selection protocols, which might adversely influence live birth rates and hence make a move towards eSET more difficult. We believe that the Association of Clinical Embryologists (ACE) has an important role to play in facilitating the development of more consistent embryo rating protocols.
- 15.3 We have also heard of concerns by clinicians that the transition to more eSET is made difficult because of the way private treatments, patient choice and league tables interact. Under the given circumstances, clinicians might find it hard to initiate the necessary change because they would risk losing patients and possibly even NHS funding if they then appear to be less 'successful' in the annual HFEA outcome data currently based on the fresh cycle only. This means that even clinicians who are convinced of the need for more eSET are not prepared to make the transition themselves, unless the whole sector moves with them. This is an argument for the need for central guidance by the professional bodies and the HFEA.
- 15.4 We have also heard from clinicians, nurses and counsellors who remain unconvinced themselves that twins are not a positive outcome for IVF. Fertility centres are often not part of comprehensive hospital environments and are remote from the obstetric complications, problems of premature and low-birthweight babies and overstretched neonatal and paediatric services. We have heard from Finnish clinicians who organised guided tours of neonatal wards for fertility doctors and nurses and asked them whether they would rather be responsible for the birth of healthy 40 week babies weighing 3000g or for the birth of 30 week twins weighing 1500g each. We are convinced that, upon reflection, most fertility practitioners in the UK would choose the former. Some members of our group even suggested that fertility centres should be charged for part of the costs incurred by the NHS for looking after premature twins who need expensive intensive care. However, it was agreed that this would not only be contrary to the principles of the NHS, but also ultimately affect fertility patients to whom the costs would be passed on.

15.5 The group also discussed briefly the incidence of twins after ovarian stimulation (without IVF, for example when conducting IUI). However, the extent of this problem is difficult to assess since IUI centres (or even GPs prescribing ovarian stimulation drugs on their own) are not required to register each treatment with the HFEA or any other regulator. The implementation of the EU Tissue Directive will bring IUI clinics into the remit of the HFEA, however the extent of the HFEA's inspections and regulatory control is still being worked out. The group therefore decided to limit its discussions and recommendations on IVF (and ICSI). Once IVF has been addressed and the Directive is in force, it might be easier to bring other fertility treatments in line with new guidance. The need to address the practices of non-IVF ART is clear, as demonstrated by a recent Belgian study on twin births after non-IVF assisted conception which found that perinatal outcome for non-IVF conceived twins was significantly and consistently worse than for naturally conceived children (both twins and singletons).⁹⁷

15.6 Summary: The UK fertility sector

- *We appreciate that not all the international data and approaches used will be directly transferable to the UK environment, as the UK fertility sector is organised along different lines.*
- *However, we believe that arguments about UK exceptionalism should not be overplayed either. More eSET cycles performed in the UK would result in fewer twins and proportionally more healthy full-term singletons. It is also possible that initially, we may have to accept a small reduction in birth rates, when based on one fresh cycle only; but that cumulative rates, which include thawed embryo transfers, would significantly redress the balance.*
- *Careful selection of both patients and embryos can maintain acceptable birth rates and reduce multiple pregnancies. International data can help inform this policy development process.*
- *The overall shortage of NHS funded IVF cycles and the huge variation across the country in access to NHS treatment make eSET more difficult to apply in the UK.*

IVF after eSET

We also discussed what IVF treatment might look like once a reduction of multiple pregnancies had been achieved. It is important to acknowledge that a reduction of multiple pregnancies does not eliminate all the risks associated with IVF.⁹⁸ There is some evidence that IVF singletons, too, have higher risks of complications and health problems than naturally conceived singletons.⁹⁹ However, the biggest risk by far for IVF children's health is their high chance of being born as part of a set of multiples.¹⁰⁰

Also, we felt it was important to recognise that it is unrealistic to expect IVF to mirror the natural twinning rate of around 1 %. Reducing the multiple rate to the naturally occurring level would – at least based on current medical practice – entail a likely drop in birth rates after IVF that will not be acceptable to clinicians and patients. However, we believe a substantial reduction of the twin rate can be achieved without significantly reducing patients' prospects of conceiving.

Furthermore, an increase in (eSET) cycles might have two broad knock-on effects on IVF as it is practised in the UK: On the one hand, it can (and hopefully will) lead to improvements in the process and protocols of embryo rating and selection and in embryo freezing and thawing. On the other hand, once women with a relatively good prognosis (young, no previous failed IVF cycles) are routinely offered eSET cycles, clinicians and patients might consider a different way of preparing patients for IVF: natural cycle IVF.

In natural cycle IVF, rather than intensively stimulating the woman's ovaries and creating a high number of embryos for freezing, the woman's ovaries are not stimulated to produce a high number of eggs. Instead, the one naturally maturing egg is extracted, fertilisation is attempted, and if it is successful, the zygote will be transferred to the woman's uterus. This method of IVF is obviously less invasive and physically demanding for the woman, but might not be appropriate for patients whose chances of an embryo actually successfully implanting in the womb are lowered (for example because of adenomyosis or fibroids).¹⁰¹ Another approach to making IVF less unpleasant and demanding for the woman is 'soft IVF' whereby the woman's ovaries are only stimulated to produce a small number of eggs, rather than the high numbers normally aimed for in IVF that aims at embryo selection and freezing.

Our group does not wish to express a preference for any particular approach to stimulation for IVF, since this is clearly a matter for the clinician and patient to determine based on the patient's circumstances and preferences. However, it is possible that natural cycle IVF might become more widely practised once eSET policies are introduced.¹⁰²

Recommendations

The expert group was tasked with developing recommendations for the HFEA. However, during the course of our discussions it quickly became apparent that the HFEA could not tackle the problem of multiple births in isolation. If progress on reducing multiple birth rates after IVF is to be made, a number of organisations need to become part of the solution. The final part of this paper lists our recommendations to the various organisations we identified as playing a role. Naturally, our recommendations for the HFEA itself are the most detailed and will be discussed first.

16. Recommendations for HFEA Guidance

16.1 The need for guidance

- 16.1.1 We discussed whether new guidance to clinics (in form of a revision of 8.20 – 8.22 of the current Code of Practice) was in fact necessary, or whether the desired change of clinical practice could be brought about through clinics acting autonomously, backed up by new professional guidance (by the RCOG, BFS and ACE). However, we agreed that the necessary change was unlikely to come about soon enough or consistently enough, since the market, the publishing of outcome data and patient views all encourage clinics to stick with multiple embryo transfer. Past experience with the introduction of the two-embryo transfer policy also shows that professional guidance alone was insufficient to shift clinical practice. What was ultimately effective was rigorously monitored and enforced HFEA guidance.¹⁰³
- 16.1.2 In early discussions, there were a number of members of our group who felt that guidance obliging clinics to move to eSET should not be issued without there also being an improvement to the NHS funding provision for IVF patients. They felt that patients, particularly in parts of the UK where they cannot access more than one IVF cycle – often without the frozen follow-on cycle – would be unduly disadvantaged by even a small possible drop in pregnancy rates. In their view, a change in guidance should be linked to full implementation of the NICE fertility guideline, with three full (fresh and frozen) cycles and no additional eligibility criteria.
- 16.1.3 The group acknowledged, however, that the NHS funding situation is outside the control of the HFEA and that difficult funding issues should not restrain improvements to clinical practice. Another reason for changing HFEA guidance was that some clinicians themselves expressed a preference for the clarity and consistency of strong HFEA guidance rather than having to negotiate this change on their own.
- 16.1.4 We agreed that the overall twin birth rate for UK IVF clinics should be brought down to below 10%. This is still a long way off the natural twin birth rate (which is between 1 and 2 %), but it would more than halve the current rate of 23.6%. We also believe that it would enable clinics with good embryo and patient selection criteria to maintain very acceptable success rates: Other European countries have shown that a twin rate of between 5 and 10% can be achieved without compromising live birth rates. Based on current figures, with 1806 twin and 38 triplet births after IVF/ICSI occurring in 2003 alone,¹⁰⁴ the envisaged reduction of the twin birth rate to under 10% would mean that around 1000 women per year would have safer, less complicated singleton pregnancies and births, rather than twin deliveries with all their inherent risks.

16.1.5 Two broad approaches to developing HFEA guidance were put forward. Both are based on the assumption that eSET needs to be made the norm in IVF treatments:

- The setting of a maximum multiple birth rate as a new standard in the HFEA's Standards for Assisted Conception Services. This maximum multiple rate could be lowered proportionally each year until a rate of (for example) less than 10% was achieved. Clinics would then be required to show evidence that they have documented procedures and evaluating systems in place that ensure that their multiple birth rate does not exceed 10%
- The development of eSET guidance in the Code of Practice which would spell out which group of patients under which circumstances should have only one embryo transferred

16.1.6 The advantages and disadvantages of the different positions on HFEA guidance are summarised in the table below.

Policy options

Policy option	Advantages	Disadvantages
<p>1. Retain status quo (i.e. do nothing)</p>	<ul style="list-style-type: none"> ■ Does not interfere with clinicians' and patients' autonomy ■ Would not impact negatively on success rates ■ Responsibility for improving clinical practice remains with clinicians and professional bodies (no over-regulation) 	<ul style="list-style-type: none"> ■ Continued high rate of premature and low birthweight twins - some will die, some of them will be severely ill with life-long health and developmental problems; continued risks for the health of mothers ■ No incentives for the sector to change its practice ■ Market forces will make it difficult to offer eSET ■ UK might fall behind internationally in attempts to improve the safety of IVF for women and their children
<p>2. HFEA to work with clinics, patients and professional bodies to increase awareness of risks of multiple births and to encourage increased use of eSET</p>	<ul style="list-style-type: none"> ■ Might strengthen self-reliance and best practice in the sector ■ Wouldn't lead to resentment by clinicians or patients, since pace of change would correspond to clinicians' and patients' willingness to co-operate ■ Wouldn't necessarily increase administrative burden (but if professional bodies and clinicians decide to tackle the problem, they would clearly have to handle some data collection and so on) 	<ul style="list-style-type: none"> ■ In all likelihood, only a few clinicians would comply ■ These clinicians might see a drop in fresh cycle birth rate compared to those who continue transferring two embryos ■ Patients might seek out clinicians who perform fewer eSET to maximise their chances to conceive in one fresh cycle ■ Incentives remain in place that prevent change ■ Didn't work when the move from 3 to 2 embryo transfer was introduced by professional guidelines only

<p>3. Set a maximum twin rate – allow clinical freedom to achieve the set target</p>	<ul style="list-style-type: none"> ■ Clinicians can work out their own selection criteria, taking account of individual patients’ needs ■ Patients can assume that they get ‘tailored’ treatment ■ Targets can be phased in over a prescribed time ■ Policy can be adjusted to new developments in practice, it won’t get out of date ■ Monitoring by results rather than by input 	<ul style="list-style-type: none"> ■ Clinics might not have commitment, capacity or resources to develop appropriate criteria ■ Might reduce birth rates, at least in the first fresh cycle ■ Possible difficulty of enforcing and penalising inappropriate practice, HFEA might need to review how to ensure compliance ■ Will create time lag before targets can be policed ■ Might lead to target driven practice which might not correspond with clinical priorities (i.e. patients might be refused or might be offered treatment choices that are target driven)
<p>4. Develop Code of Practice guidance that defines in which cases only one embryo should be replaced, based on for example age, number of previous treatment cycles, medical history and possibly embryo quality</p>	<ul style="list-style-type: none"> ■ Clarity ■ Enforceability (perhaps apart from embryo quality) ■ Certainty about reduction of multiple pregnancy rates over a short timeframe ■ Guidance allows some degree of flexibility for clinicians, but it is limited ■ Level playing field for clinics 	<ul style="list-style-type: none"> ■ Possible resentment from clinicians and patients since it would reduce flexibility and clinical discretion ■ Might reduce success rates, particularly for poor prognosis patients, if the guidance criteria were not sufficiently flexible ■ If further treatment cycles are needed, many patients would not have access to further NHS funding; costs for private patients would also increase ■ Evidence base is not equally strong for all the criteria that would need to be included in the guideline, for example embryo quality is not judged uniformly, which would make it difficult to enforce ■ Clinics or patients might challenge guidance through the courts

16.2 Changing HFEA policy – setting a maximum twin birth rate or defining conditions for eSET?

16.2.1 Given that options 3 and 4 will require actual policy development work for the HFEA they merit a more detailed discussion. The international experience (as discussed) shows that there are a number of strategies that can successfully be adopted to reduce the number of multiples after IVF. The group did not decide whether option 3 or 4 above were preferable, but there was agreement that the status quo is no longer an option and that option 2 is probably ineffective.

16.2.2 Based on the international data the group discussed, it appears that eSET performed in 50% of cycles can achieve a twin rate of around 10%. Thus, were there to be **a target that the twin rate for each clinic was not to exceed 10% (option 3)**, it is to be expected that clinics would eventually end up performing eSET in at least 50% of their cycles, but clinics could develop their own practice-based criteria for which group of patients they think would most benefit from eSET or DET cycles.

- In all likelihood, poorer prognosis patients would still be offered two embryo transfer, with better prognosis patients having only one embryo transferred in the first instance.
- Because of the inherent unpredictability of fertility treatment, it might be difficult for clinics to be expected to hit a precise target. So the question arises how the HFEA would deal with clinics which, for example, end up with a twin rate of 15%. It might be argued that this discrepancy is just the unpredictable effect of chance alone. In practice, if a clinic clearly misses the maximum twin rate set by the HFEA, the HFEA (or one of its Licence Committees) would want to see evidence from the clinic for the criteria they use to distinguish good and poor prognosis patients, possibly drawing on the example of other clinics which were more successful at staying below the maximum twin rate.
- Practices and procedures would have to be developed by HFEA Licence Committees to compare multiple embryo transfer rates and outcomes between clinics. Consistent failure to reduce multiple embryo transfer rates would have to incur penalties for the clinic (for example imposing a mandatory minimum eSET rate).
- This policy option might also mean that different approaches to reducing the number of twin pregnancies could be ‘piloted’ by different clinics and their effectiveness and reliability could be compared, with mutual learning inside the fertility sector as a whole.

16.2.3 Were the HFEA, on the other hand, to develop **detailed guidance for the Code of Practice (option 4)** on which group of women should be restricted to eSET, the politics would differ, but the mathematics remain unchanged.

- If eSET was made compulsory for women under 35 (up to their 35th birthday), this would represent 47.5% of all the cycles performed in 2003/4. In light of the international experience referred to above (50% of eSET cycles reduce the multiple rate to 10%), this would probably not be a sufficient proportion of eSET cycles to achieve a target of 10% or less for twins, given that some women under 35 would have a less good prognosis – for example they already had a number of failed attempts – and would therefore more appropriately be offered DET.

- If the guidance addressed women aged 35 and under (i.e. up to their 36th birthday), this would represent 56.5% of all treatment cycles;
- If eSET was prescribed to all women aged 36 and under (up to their 37th birthday), this would comprise 64.6% of all treatment cycles.

16.2.4 This option (eSET for women under a certain age limit, in their first two cycles) would not take account of embryo quality. Because embryo quality is not judged uniformly across UK clinics, and because the HFEA cannot judge embryo quality in assessing a clinic's compliance with guidance, it would be difficult to include embryological criteria in the guidance. Clinics however would of course have to develop embryo selection criteria to choose the single embryo that promised best treatment outcomes and to choose embryos with sufficient quality for freezing and thawing.

16.2.5 It also seems feasible (and some group members thought it was promising) to **combine the two approaches**. For example, clinics could be given a timeframe during which they are expected to reduce their multiple rate to below 10%. If a clinic does not achieve a sufficient reduction, it would have more rigid HFEA guidance imposed on it (eSET selection criteria). This way, clinicians might be motivated to protect their autonomy (and success rates) by developing effective patient and embryo selection criteria that work for their case mix and practice.

16.3 Legal perspectives on possible new HFEA guidance

16.3.1 Since the expert group was set up to give advice principally to the HFEA, it also spent some time discussing legal implications of any new guidance the HFEA might develop and issue. Clearly, the HFEA would want to avoid the risk of litigation if guidance was opposed in some quarters.

16.3.2 The legal advice the group received was that the HFEA has a wide discretion as to the type of guidance it can develop. Both the setting of overall targets (i.e. clinics would be obliged to adhere to a multiple births rate of, for example, no more than 10%) and the setting of selection criteria for single embryo transfer policies (i.e. women aged 35 and under should have only one embryo replaced in the first two cycles) would in principle stay within the legal remit of the HFEA as a regulatory body.

16.3.4 As with all regulation of medicine and healthcare, patient and clinical autonomy have to be carefully weighed up with the regulatory aim of reducing multiple birth rates. In practice this means that any guidance the HFEA might develop cannot be applied without consideration of possible exceptional circumstances and the individual aspects of any particular case.

16.3.5 The HFEA has two principal functions in developing and enforcing policy. On the one hand the Authority is a policy making body that has to engage in a rational and transparent process (including the involvement of all relevant stakeholders) in order to reach a policy decision. On the other hand, the Authority has Licence Committees that have to oversee clinics' compliance. Licence Committees are not bound by Authority policy, but will take existing policy into account when making decisions about individual clinics or cases.

16.3.6 The feasibility of issuing embryo transfer policies and of enforcing the policy in the case of an individual clinic that wanted to step outside of HFEA guidance was confirmed in *R. (on the application of ARGC and H) v. HFEA* [2002] EWCA Civ 20.

16.4 Summary on HFEA policy options

- *The group agrees that the status quo is no longer an option. The increase in twin births and the severity of the complications after multiple embryo transfer mean that the sector's practice has to change: eSET needs to be made the norm. Because of the nature of the UK fertility sector, it will only change quickly and consistently if compelled to do so by HFEA guidance.*
- *We discussed in detail the advantages and disadvantages of two principal approaches: setting a maximum twin rate or developing guidance for eSET cycles.*
- *We also considered that the approaches could be combined or further refined - we feel that the views of stakeholders would be useful to fine-tune HFEA guidance.*
- *We recommend that the national IVF twin rate should be rapidly brought down to below 10%. This has been achieved in some European countries without a reduction in IVF birth rates.*

17. Recommendations for HFEA inspections and risk management of clinics

We believe that the HFEA inspectorate has an important role to play in raising awareness of the problem of multiples in the sector and in fostering best practice:

- All inspectors visiting a clinic should be aware of the clinic's multiple rate and their use of fetal reduction.
- Where triplet births have occurred, these should be discussed with the clinic as part of the inspection process.
- All clinics should be required to work up (and produce evidence for) policies for reducing multiple pregnancy, including patient information.
- Inspections should discuss the clinic's embryo rating procedures, eSET policies and cryopreservation protocols.
- As part of the patient feedback, patients should be asked whether the risks of multiple births were discussed with them and whether eSET was offered to them as the treatment of choice.
- Where clinics have a higher than average multiple rate, this should be considered a 'risk factor' for the purposes of the HFEA's internal risk rating procedures ('risk matrix'), by which inspections are targeted at the most risk prone clinics.
- Inspection reports that are now published should refer to a clinic's multiple rates and should highlight why they are considered a risk factor.
- Clinics should be encouraged to share data on their eSET and embryo rating policies with other clinics in order to facilitate best practice development across the sector.

18. Recommendations for HFEA communication work

- 18.1 Collecting and publishing information about the UK fertility sector is an important function of the HFEA. Information about the risks and frequency of multiple births needs to be emphasised in all of the HFEA's communications, particularly if changes to HFEA guidance are introduced.
- We recommend that the HFEA investigates ways of making the singleton live birth rate after IVF the headline figure in its annual outcome presentation. Multiples should be considered a complication, not a success.
 - Further, the HFEA should consult the fertility sector and the relevant stakeholders about ways of presenting the overall quality of a clinic's performance (star rating etc) in a balanced way, which would include its multiple rates in order to develop a more rounded overall assessment of clinics.
 - The patient guide and other relevant patient information should include detailed information and personal experience about the reality of having premature twins after IVF.
- 18.2 Some desirable changes are outside of the HFEA's own remit. However, the HFEA has a role to play in convincing other organisations of the need for change:
- It should work together with professional bodies, patient groups and clinics in order to promote action on the problem of multiple births.
 - The HFEA should send a clear message to the Department of Health on how the lack of NHS funded fertility services contributes to many of the problems of the sector, and how the failure to implement the NICE fertility guideline is a major obstacle to reducing multiple birth rates in the UK.
 - It should investigate the possibility of providing information to PCTs about commissioning eSET IVF cycles as a way of reducing the healthcare burden caused by prematurity after multiple births.
 - It should press for a relaxation of the HFE Act confidentiality restrictions as part of the Review of the Human Fertilisation and Embryology Act 1990 in order to facilitate research on the wider health outcomes for IVF children.

19. Recommendations for clinics

The IVF clinical team has the largest role to play in reducing the number of multiple births after IVF. They need to be aware of the risks of twin birth and be committed to reducing their incidence as part of good clinical practice. If clinicians, embryologists, nurses and counsellors do not change the way they work, progress will not be made.

- Clinics are obliged under section 13 (5) of the HFE Act to consider the welfare of the child or children born after IVF treatment. In our view, this means that the child's chances to be born full-term and with a healthy birth weight should be maximised. Clinicians who prefer to continue transferring two embryos, even for good prognosis patients (who will have the highest chance of getting pregnant and of conceiving twins) should consider how this preference can be reconciled with their legal obligation to take into account the future child's welfare.
- Clinical embryologists need to develop embryo rating and cryopreservation policies with a focus on increasing the proportion of cases in which eSET is performed.
- Charges in private clinics should encourage patients to consider eSET, for example by including the cryopreservation of spare embryos (and possibly subsequent frozen/thawed cycles) in the unit price for a cycle of IVF.
- Patient information and counselling needs to focus on the reality of having premature twins and the obstetric complications of multiple pregnancy.

20. Recommendations for professional bodies

- 20.1 It is clear from the available evidence that eSET can be offered to a significant sub-group of patients without jeopardising live-birth rates. This is why our group believes that HFEA guidance needs to change in order to reflect this growing evidence base. However, it is clear to us that further work would be beneficial in order to clearly and reliably identify those patients who would benefit the most from eSET, but also those patients for whom DET still remains the best option.
- 20.2 We believe that the professional bodies are best placed to review the available evidence, identify gaps and develop detailed guidance on the exact characteristics of those women and embryos that are most appropriate for eSET. We believe that the professional bodies could usefully complement the available international evidence by reviewing the existing data from UK practice.
- The British Fertility Society (BFS), the Royal College of Obstetricians and Gynaecologists (RCOG) and the Association of Clinical Embryologists (ACE) all should collaborate to review the existing evidence on eSET and develop evidence based guidelines containing selection criteria for women and embryos that are most suitable for eSET.
 - The RCOG and the Royal College of Paediatrics and Child Health (RCPCH) should also continue to collate and communicate the data on the risks of multiple pregnancy and birth and the difficulties caused for children's services by the high incidence of multiple births after IVF.
 - The Royal College of Nursing (RCN) Fertility Nurses Group and the British Infertility Counselling Association (BICA) can, based on their extensive experience with treating and counselling fertility patients, make a helpful contribution to developing better practice, including better protocols and materials, for the communication of the risks of multiple pregnancies.
 - All the professional bodies should work together with patient organisations in order to campaign for better access to publicly funded fertility treatments.

21. Recommendations for the Department of Health

21.1 The Department of Health has an important role to play in promoting the acceptance of an eSET policy. In seeking to influence the commissioning decisions of local health communities the following factors should be emphasised:

- The significant effect that multiple births after IVF have on public sector services in the short, medium and long-term. These consequences are borne in the short or medium term by neonatal and paediatric units and in the longer term by social support, health and education services. This places an additional strain on an already stretched system.
- Whilst local prioritisation processes are essential, the piecemeal adoption of the minimum standard described by the Secretary of State in 2004 is unfair and unacceptable to patients. Central advice should reflect the political priority previously ascribed to these services, possibly through the issuing of a health service circular to commissioning organisations outlining the minimum acceptable standard for IVF/ICSI provision.
- Policies should be amended with immediate effect to ensure that cryopreservation and the use of frozen embryos are included in the package of care as recommended by the Secretary of State in February 2004.

21.2 Acceptance by patients and clinicians of the progress needed to reduce multiple birth rates will be much more difficult to achieve if the NICE guideline is not implemented and the current under-funding and inequity of provision of fertility services is not addressed. Different mechanisms apply in Scotland¹⁰⁵ and Northern Ireland,¹⁰⁶ but there too, fertility services have been ranked against other services competing for resources, albeit to a lesser extent than in England. The absence of 'ring fenced' funding calls into question the presumed political imperative to raise the status of fertility treatments. National agreement on criteria for fertility provision would greatly enhance patient confidence in the NHS and allow a consistent approach to be adopted between clinics.

21.3 Through the planned Review of the HFE Act, the DH should address the need for follow-up studies by relaxing the additional confidentiality restrictions imposed by section 33 HFE Act which make it impossible to use HFEA register data for epidemiological follow-up studies of IVF children. Finally, it would help if the information collated and published by the Department of Health on abortions in the UK would clarify whether and where the fetal reductions included in the data comprise abortions for fetal abnormality.

22. Recommendations for the NHS/ PCT commissioners

This report has repeatedly made the point that the current inconsistent, patchy provision and general under-funding of fertility services is a significant obstacle to the effective implementation of eSET policies in the UK. NHS commissioners have an important role to play in creating an environment conducive to the required change. We have been convinced that improved funding for fertility treatment would be offset by a reduction of morbidity and mortality after multiple pregnancy and birth. We therefore recommend that:

- Immediate action should be taken to include cryopreservation (and also the subsequent frozen/thawed embryo transfer) in the commissioning of an IVF cycle in order to increase acceptance of eSET by clinicians and patients.
- Those PCTs that have yet to implement even the one cycle of IVF (including frozen follow on cycles) need to do so as quickly as possible. All PCTs need to have plans in place to implement the NICE fertility guideline fully.
- In the meantime, PCTs should work with INUK whose survey aims to gather baseline information about fertility provision in the whole of the UK.
- PCTs should take into account the overall twin and triplet rate of individual clinics when reviewing contracts for provision of infertility services, and should consider withholding contracts from clinics likely to place significant strain on NHS funded obstetric and neonatal services due to excessively high numbers of multiple pregnancies.
- The multiple pregnancy rate for non-IVF fertility services should also be reviewed when commissioning IUI and other fertility treatments.
- Commissioning of IVF should include a requirement for eSET as the norm for the appropriate patient group and/or maximum multiple birth rates as a target in order to introduce the required changes to clinical practice. This would serve as a quality beacon for the private sector.

23. Recommendations for NICE

When revisiting its fertility guideline the National Institute for Health and Clinical Excellence should:

- Investigate the feasibility of eSET for the majority of fertility patients.
- Evaluate the health economic consequences of eSET and DET by including the healthcare costs incurred by often premature and low-birthweight multiple births.
- Emphasise the importance of cryopreservation and re-iterate that freezing of embryos needs to be made part of the standard IVF package of care.

24. Recommendations for patient groups

We recognise that the problem of multiple births places patient groups such as Infertility Network UK in a difficult position. On the one hand they lobby for better access to and quality of fertility services; yet eSET policies might well reduce patient's initial chances of pregnancy on the first fresh IVF cycle, which might be the only cycle they have funding for. On the other hand they also have an interest in making IVF safer and a better experience for patients, which means they also have an interest in reducing the instances of complications caused by multiple pregnancy and birth. We therefore recommend that patient groups:

- Continue their effective campaigning for better public funding for fertility services and highlight the knock-on problems that are caused by the pressures patients find themselves under (including the pressure to have more than one embryo put back).
- Continue and improve their information work on the risks of multiple births in order to educate patients of the need for change.
- Emphasise the point that, as is the case for fertile couples, fertility patients should be able to complete their families with singleton pregnancies and one child after the other. They should not have to compromise on safety and quality of treatment because of financial pressures. The move towards eSET should not be seen as fertility patients being entitled to less, but being entitled to more: safer, better IVF treatment with better chances of having healthy children in the end.

25. Recommendations for researchers/ academics

There is a wealth of data on the risks for premature and low birthweight children and the increased risks of morbidity and mortality for twin and higher order births. However, we found a lack of data that views the problem from the starting point of fertility treatments. There are, therefore, not many figures on the relative or absolute risk of complications or disability a fertility patient faces when making decisions about eSET or DET. We therefore recommend that:

- The available data on risks for twins needs to be evaluated and represented taking the decision for eSET or DET as a starting point; this would help communicate the need for change to policy makers, patients and clinicians.
- There should be more systematic follow-up of the health outcomes for children after fertility treatments, in particular of twins and higher order births; attempts to unify and extend the data collected on neonatal care and outcomes, for example the recently set up South of England Neonatal Data System (SEND),¹⁰⁷ might provide a good opportunity for this much needed follow up of IVF children.
- In order to make this research possible, methods need to be found that work around the existing confidentiality restrictions limiting the use of HFEA register data.¹⁰⁸
- There is a need to explore and evaluate the long-term consequences and effects of fetal reductions on children and families.

Conclusion

26. The expert group on multiple births after IVF was set up in order to advise the HFEA on the risks of multiple births after IVF and possible actions the HFEA might adopt in order to tackle these risks.
27. We have analysed a wide range of causative factors and made a number of recommendations, not solely addressed at the HFEA. Our analysis can be summarised as follows:
 - Making the move from two embryo transfer to a predominance of eSET in the UK context will not be easy, because several factors act as disincentives; amongst these are the current inconsistent funding arrangements for fertility services, the failure to implement the NICE guideline on fertility treatments, and the way the UK sector is organised.
 - However, maintaining the status quo is no longer an option. The fertility sector has for too long been responsible for the creation of children with complex needs: IVF children deserve the best possible chance to be born at full term and as healthy singletons. The only way this can be achieved is by making eSET the norm: those women with the highest risk of having twins need to only have one embryo transferred during IVF.
 - The biggest change has to happen in fertility clinics, but the required culture change would be greatly helped if there was a clear steer from the Department of Health to PCTs that they must fully implement the NICE guideline, which stated that three cycles of IVF should be made available on the NHS, including the cost of cryopreservation and frozen/thawed cycles.
 - We believe that if those we have identified as having a role to play adopt our recommendations, the UK fertility sector would be improved in several ways; be more rationally funded, and safer for women and their children.

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- ² Some information about the group's work on the HFEA website, under the Policy section (which is to be found in the 'how we regulate' section).
- ³ An analysis of as yet unpublished and unverified HFEA register data shows that the incidence of triplets has more than halved since the strict 2 embryo policy was introduced, this drop is mostly attributable to women under 40: In 2003/4 there were 33 triplet births in women under 40, 16 of these after triple embryo transfer. In 2004/5 there were 12 triplet births in women under 40, with no triple embryo transfers in this age group. Also see Simmons, R et al. Dramatic reduction in triplet and higher order births in England and Wales *BJOG* 2004; 111: 856 – 858.
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¹⁰² Based on the latest verified figures, between 2002 and 2004, around 2% of IVF in the UK was ‘natural cycle’ with a live birth rate of 18.3 %.

¹⁰³ As outlined above, HFEA guidance is not compulsory in the sense that a breach of guidance automatically triggers sanctions. However, breaches would be considered by HFEA licence committees which would ask for an explanation. Ultimately, serious or repeated breaches can be sanctioned through revocation of the clinic’s licence. On past experience with HFEA regulation vs professional self-regulation also see English, V. Autonomy versus protection – who benefits from the regulation of IVF? *Human Reproduction* 2006; 21: Advance Access, 2 August 2006.

¹⁰⁴ HFEA register data, 2003, IVF and ICSI triplet, twin and singleton birth events.

¹⁰⁵ In February 2000, the Expert Advisory Group on Infertility in Scotland (EAGISS) published guidance on the treatment of infertile couples. The guidance included eligibility criteria for treatment and, among other recommendations, stated that eligible couples should receive a maximum of three cycles of IVF. In March 2003, a National Consensus meeting was held to discuss recommendations to update the eligibility criteria. These recommendations were taken forward for public consultation, the outcome of which is currently awaited.

¹⁰⁶ Since December 2001, an interim service has been in operation in Northern Ireland that has made fertility services available on a limited basis to couples. A public consultation document entitled “From People to Parents”, on the longer term provision of fertility services was issued by the Department of Health, Social Services and Public Safety in October 2003. A policy decision was recently announced: women under 40 will be entitled to 1 cycle of IVF, with no additional eligibility criteria above those comprised in the NICE guideline itself.

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Bardis, N et al. Modes of conception and multiple pregnancy: a national survey of babies born during one week in 2003 in the United Kingdom *Fertility and Sterility* 2005; 84: 1727 – 1732
Study collecting data on every baby born in one week in the UK with respect to mode of conception, multiplicity of pregnancy, and outcome. Finds that the multiple rate is much higher in pregnancies that were achieved with assistance, the majority of these are due to IVF, rather than clomifene citrate therapy (ovulation induction without IVF). Concludes that multiple pregnancy from IVF remains a significant problem and contributes a greater burden than ovulation induction therapies to the NHS. 38.1% of the twins were admitted to special care baby units.

Bergh, C. Single embryo transfer: a mini review *Human Reproduction* 2005; 20: 323 – 327
Review of four randomised controlled trials and seven observational studies evaluating outcomes after SET versus DET. Concludes that in good prognosis patients satisfactory delivery rates can be achieved with eSET. The RCTs show a significantly lower delivery rate after eSET, but which might be restored with the addition of frozen-thawed embryo transfers. Observational studies show the same pregnancy rates after SET and DET. The reason for achieving similar results is that the two groups are not strictly comparable; good prognosis women receive eSET while poor prognosis women receive DET.

Bertarelli Group Infertility therapy-associated multiple pregnancies (births): an ongoing epidemic. *Reprod Biomed Online* 2003; 7: 515 – 542

Report from an international consensus meeting on the need to reduce the number of multiple births after ARTs.

Bhattacharya, S and Templeton, A. What is the most relevant standard of success in assisted reproduction? *Human Reproduction* 2004; 19: 1939 – 1942
Discussion article on the evidence of success rates after eSET and DET and its interpretation. Highlights the need to take context specific information (for example about funding or the availability of freezing programmes) into account and warns against over-generalisation of the available data.

Bhattacharya, S and Pandia, Z. Assisted conception and multiple pregnancies: methods of reducing multiples from assisted reproduction in: *Multiple Pregnancy* Kilby M *et al* (eds) RCOG 2006
Overview chapter describing the risks of iatrogenic multiple pregnancy (including higher order multiples) in assisted conception, examining the factors that encourage multiples and reviewing the literature on the effect of embryo number on IVF outcome.

Blake DA et al. The merits of blastocyst versus cleave stage embryo transfer: a Cochrane review *Human Reproduction* 2004; 19: 795 – 807
Review of the available good quality data comparing blastocyst and early stage embryo transfer. Finds no significant difference in success rates.

Blennborn, M et al. The couple’s decision-making in IVF: one or two embryos at transfer? *Human Reproduction* 2005; 20: 1292 – 1297
A Swedish study investigating the decision making process and the factors influencing the decision to have eSET or DET amongst 274 IVF patients. Finds that the patients have a good knowledge of the risks of multiple pregnancy. Around 60% of couples chose DET, 40% SET. Younger age and shorter duration of infertility, but most importantly the experience of previous childbirth and spare embryos to freeze were factors leading couples to choose SET, whereas perceptions of higher success rate and previous IVF attempts were factors indicating a preference for DET.

Blickstein I. Epidemiology of cerebral palsy in multiple pregnancies in: *Multiple Pregnancy* Kilby M et al (eds), RCOG 2006

Overview article examining the causes and incidence of cerebral palsy in twins. The most important factor for the increased risk of CP for twins is prematurity. US data for 2003 showed that 11.9% of twins and 36.1% of triplets are born very premature (before 32 weeks of gestation) or very low birth-weight (less than 1500g). Estimates that IVF with three embryo transfer cause an excess of 14 babies per 10000 who are born with CP – IVF with 2 embryo transfer still causes an excess of 6 babies born with CP. This excess is due to multiples being born prematurely and therefore at increased risk of CP.

Blondel, B et al. The impact of the increasing number of multiple births on the rates of preterm birth and low birth weight: an international study *American Journal of Public Health* 2002; 92: 1323 – 1330
Analysis of international birth certificate data assessing the impact of multiple births on the overall perinatal health indicators preterm birth and low birth weight. Found that although triplets had a very high relative risk of being born very prematurely and light, they account only for a small proportion of preterm and low-birthweight newborns. However, twins accounted for a significant proportion of preterm and low-birthweight newborns. In different countries ART account for between 2 and 30% of all twin births.

Blondel, B and Kaminski, M. Trends in the occurrence, determinant, and consequences of multiple births *Seminars in Perinatology* 2002; 26: 239 - 249

International review analysing birth register data on rising multiple rates. Finds that between one fourth and one third of the increase in twin and triplet pregnancies is due to the concurrent increase in maternal age (older women are more likely to have multiple pregnancies than younger ones). Estimates that in recent years the contribution of ART (excluding ovarian stimulation) on the number of twin pregnancies internationally ranges from between 10% and 24%, and 22% to 59% for triplets. Identifies prematurity as the biggest public health risk in multiple pregnancies. About half of twins and more than 90% of triplets are born under 37 weeks of gestation or under 2500g at birth.

Buitendijk, S et al. Indicators of fetal and infant health outcomes *European Journal of Obstetrics and Gynecology and Reproductive Biology* 2003; 111: S66 – S77

Review of the available European perinatal data to, firstly, assess feasibility of implementing a uniform reporting and register system for perinatal health outcomes and to, secondly, provide an overview of health outcomes according to the information already available. Establishes the important impact of preterm births on perinatal health outcomes and public health systems. 'Although only approximately 1% of births are very preterm, they constitute an important challenge for health systems, as they require highly specialised care to achieve optimal health outcomes. Births before 32 weeks' gestation account for 35 – 60% of neonatal deaths.' 'A focus on multiple births is also important, since neonatal mortality is six to seven times higher for babies from multiple pregnancies than from singleton pregnancies.' Links increase of multiple births to increased use of ART.

Bryan, E. The impact of multiple preterm births on the family *BJOG* 2003; 110: 24 - 28

Overview article summarising the known risks for twins and their families: parents of twins have been shown to be less responsive to their infants, parental stress has been demonstrated to be higher. There is a higher incidence of behaviour problems, even amongst siblings of twins, more depression and more child abuse.

Bryan, E and Denton, J. Special consideration of twins and higher order births in: Sutcliffe, AG (ed.) *Health and welfare of ART children* informa healthcare 2006

Overview chapter reviewing the literature on twins or higher order multiples after fertility treatment. Discussing medical and psychosocial problems, the issue of multifetal pregnancy reduction and further research needs.

Campbell, DM and Templeton, A. Maternal complications of twin pregnancy *International Journal of Gynecology and Obstetrics* 2004; 84: 71 – 73

Population based study reviewing all the singleton and twin births in the Grampian region of Scotland between 1976 and 1999 in order to assess the increased relative risks of multiple vs. singleton pregnancy for the woman herself. Finds 2 to 3 fold increase in obstetric complications, both mild and serious and threefold increased risks of mortality.

Child TJ et al. The desire for multiple pregnancy in male and female infertility patients *Human Reproduction* 2004; 19: 558 – 561

Prospective questionnaire study of around 800 patients' attitudes to multiple pregnancy. Finds that a significant proportion (41%) of fertility patients consider multiple birth an ideal treatment outcome. Recognition of the increased fetal risks of multiple pregnancy significantly reduced this desire. Patient education may play an important role in assisting physicians in the quest to reduce the contribution of assisted reproductive treatment to multiple births and their attending complications.

Chitayat D and Hall JG. Genetic aspects of twinning in: *Multiple Pregnancy* Kilby M et al (eds), RCOG 2006

Overview article discussing the genetic basis for twinning. Finds that monozygotic twinning is also increased after fertility treatments for unknown reasons.

Cohen, J. Procreative tourism and reproductive freedom *RBM Online* 2006; 13: 145 - 146

Opinion piece that presents reproductive tourism not as a problem that needs to be tackled, but as an expression of infertile couples' moral autonomy.

Colpin, H et al. Parenting stress and psychosocial well-being among parents with twins conceived naturally or by reproductive technology *Human Reproduction* 1999; 14: 3133 – 3137

Small study comparing parenting stress and psychosocial well-being among parents with 1 year old twins conceived naturally or by reproductive technology. Finds that first-time mothers with a history of infertility obtained significantly higher stress scores for parental competence and health and showed lower psychosocial well-being compared with naturally conceiving first-time mothers and mothers with a history of infertility who already had children.

Cook R et al. A preliminary study of parental stress and child behaviour in families with twins conceived by *in-vitro* fertilisation *Human Reproduction* 1998; 13: 3244 – 3246

A small scale qualitative study of parenting quality, parental stress and child behaviour in families with twins conceived by IVF in comparison with families with naturally conceived twins. No differences were found between the types of family in parenting quality or child behaviour. However, parents whose twins were conceived by IVF reported greater stress associated with parenting than parents with naturally conceived twins.

Costeloe, K et al. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability *Pediatrics* 2000; 106: 659 – 671

Big multi-centre study evaluating the outcomes for all infants born before 26 weeks of gestation in the UK and the Republic of Ireland between March 1 1995 and December 31 1995. This report is of survival and complications up until discharge from hospital. Less than one in four infants were admitted to intensive care (the others died before admission). Overall survival of those who were admitted was 39%. Of the survivors, 62% had one or more cerebral cyst and/or hydrocephalus, treated ROP (retinopathy of prematurity – an eye problem), or ongoing oxygen dependence at their predicted due date. The study points at fertility treatments as the likely cause of the high proportion of multiples in the study group.

Criniti, A et al Elective single blastocyst transfer reduces twin rates without compromising pregnancy rates *Fertility and Sterility* 2005; 84: 1613 – 1619

Single centre observational study reviewing outcomes for 238 blastocyst cycles where either one or two blastocysts were transferred. Finds no difference for pregnancy rates, but a striking difference for the twinning rate, with 62% of pregnancies after two blastocyst transfer being twin pregnancies, compared to 3.2% after single blastocyst transfer.

Ellison, M and Hall J. Social stigma and compounded losses: quality of life issues for multiple birth families *Fertility and Sterility* 2003; 80: 405 – 414

Small qualitative study analysing the experience of IVF parents of twins and higher order births. Finds that the often lengthy and traumatic experience of infertility and its treatment can impact on people's eventual parenting experience. This can be compounded by previous pregnancy loss, miscarriage or fetal reduction.

Ellison, M et al. Psychosocial risks associated with multiple births resulting from assisted reproduction *Fertility and Sterility* 2005; 83: 1422 – 1428

Comparing US mothers of IVF conceived singletons, twins and triplets, the study finds that for each additional multiple birth child, the odds of having difficulty meeting basic material needs more than triple and the odds of lower quality of life and increased social stigma more than double. Each increase of multiplicity is also associated with increased risk of maternal depression.

El-Toukhy, T et al. IVF results: optimise not maximise *American Journal of Obstetrics and Gynecology* 2006; 194: 322 – 331

Review of articles published in English between 1990 and 2004, summarizing the risks and complications related to multiple pregnancies and exploring possible strategies such as blastocyst culture, pre-implantation genetic screening and embryo cryopreservation which can help implementing single embryo transfer policies in order to reverse the tide of multiple pregnancies without reducing the good success rates that modern IVF treatments enjoy.

English, V. Autonomy versus protection – who benefits from the regulation of IVF? *Human Reproduction* 2006; 21, Advance Access 2 August 2006

Comment article discussing the value of regulation by the HFEA for patients and the sector.

ESHRE Task force on Ethics and Law. Ethical issues related to multiple pregnancies in medically assisted procreation *Human Reproduction* 2003; 18: 1976 – 1979

This sixth statement of the ESHRE Task Force on ethics and law discusses the ethical issues raised by multiple pregnancies resulting iatrogenically from the use of medically assisted procreation. The incidence of multiple pregnancies and the consequences for the child are discussed, together with general and specific ethical issues. Four recommendations are made – single embryo transfer, public funding for assisted reproduction, multiple pregnancies reported as complications not successes, and a uniform method of presenting results.

The European IVF-monitoring programme (EIM) for the European Society of Human reproduction and Embryology (ESHRE) Assisted reproductive technology in Europe 2002. Results generated from European registers by ESHRE *Human Reproduction* 2006; 21: 1680 – 1697

Sixth report summarising the results of assisted reproductive techniques from treatments initiated during 2002 in 25 European countries.

Gardner, D et al. Single blastocyst transfer: a prospective randomised trial *Fertility and Sterility* 2004; 81: 551 – 555

A small American randomised trial comparing single and double blastocyst transfers in 48 women. Single blastocyst transfer maintains very high success rates (60.9%) with no twins, compared to 76% after double transfer, with a twinning rate of 47.4%.

Gerris, J. Single embryo transfer and IVF/ICSI outcome: A balanced appraisal *Human Reproduction* 2005; 11: 105

Review of the available evidence on multiple births after IVF and SET as a strategy for reducing the iatrogenic twin rate. Emphasises the importance of good selection criteria for patients suitable for SET and for embryos with a high putative implementation potential.

Gerris, J et al. Prevention of twin pregnancy after IVF or ICSI based on strict embryo criteria: a prospective randomised clinical trial *Human Reproduction* 1999; 14: 2581 – 2587

A prospective randomised study comparing eSET with DET in a group of selected patients (under 34, first cycle, at least 2 good quality embryos) on the basis of retrospectively delineated embryo selection criteria. A good quality embryo was defined as having 4 or 5 blastomeres on day 2 and at least 7 blastomeres at day 3 after insemination, the absence of multinucleated blastomeres and < 20% cellular fragments on day 2 and day 3 after fertilisation. The study shows that the ongoing pregnancy rate was higher in the double embryo transfer group than in the single embryo transfer group (74.1 versus 38.5%). However, the ongoing pregnancy rate in the SET group was still equal to or higher than the generally accepted monthly fecundity rate of couples with normal fertility.

Gibson, M. Outcomes with assisted reproductive technology: Shooting first, asking questions later *Obstetrics and Gynecology* 2004; 103: 1142 – 1143

Editorial discussing various adverse effects for infant health after IVF. Identifies multiple gestation as the 'most important burden imposed through ART' for public health.

Glazebrook, C et al. Parenting stress in first-time mothers of twins and triplets conceived after *in vitro* fertilisation *Fertility and Sterility* 2004; 81: 505 – 511

A prospective cohort study of 260 first-time mothers, finding that one year post-partum, 22% of mothers of multiples had Parenting Stress Index scores indicating severe parenting stress, compared with 5% of mothers of IVF singletons and 9% of mothers of naturally conceived singletons. Also finds significantly higher complication rates for multiple births.

Groothuis, J et al. Increased Child Abuse in Families with Twins *Pediatrics* 1982; 70: 769 – 773

US cohort study of children born in one hospital, comparing outcomes for twins and singletons, finding a significantly higher incidence of abuse for twins.

Haggart, P et al. Effect of B vitamins and genetics on success of in-vitro fertilisation: prospective cohort study *Lancet* 2006; 367: 1513 – 1519

Prospective cohort study of 602 women undergoing fertility treatment and 932 women who conceived naturally, investigating the role of B vitamins and genetic variations for the success or otherwise of IVF. Outcomes: Women with certain genetic variations are less likely to conceive after IVF. Women with higher concentration of folate in their blood were slightly more likely to have twins. Proposals to fortify the UK diet with folic acid could lead to a small increase in the number of twins born after IVF.

Hartshorne, GM and Lilford, RJ. Different perspectives of patients and health care professionals on the potential benefits and risks of blastocyst culture and multiple embryo transfer *Human Reproduction* 2002; 17: 1023 – 1030

A small study comparing clinicians', embryologists' and patients' views on embryo transfers, multiple pregnancies and blastocyst culture. It finds that patients were willing to take greater risks of multiple

pregnancy after blastocyst transfer than the professionals involved deemed appropriate

Helmerhorst, FM et al. perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies *BMJ* 2004; 328: 261 – 265

A systematic review of controlled studies published between 1985 and 2002 comparing perinatal outcomes of single and twin pregnancies achieved by IVF or conceived naturally. Outcome: IVF singletons fare worse than naturally conceived singletons. This is not the case for twins – where IVF twins fare slightly better (this might be because of chorionicity), but this is ‘poor consolation for the much greater risks of twin pregnancies overall. Virtually all perinatal and infant morbidity occurs more frequently in twins than in singletons.’

Henderson, J et al. Economic implications of multiple births: inpatient hospital costs in the first 5 years of life *Archives of Disease in Childhood Fetal and Neonatal Edition* 2004; 89: F 542 – 545
Study that applied speciality based data from the English Department of Health’s NHS Trust Financial Returns to admissions recorded in the Oxford record linkage study during 1970 – 1993 in order to assess the cost to the NHS of inpatient care for multiple births. Finds that twins spend on average twice as long in hospital as singletons, and triplets eight times as long, consequently, inpatient care for a twin is more than twice as expensive than care for a singleton.

Henman, M et al. Elective transfer of single fresh blastocysts and alter transfer of cryostored blastocysts reduces the twin pregnancy rate and can improve in vitro fertilisation live birth rate in younger women *Fertility and Sterility* 2005; 84: 1620 – 1627.

Prospective non-randomised cohort study comparing pregnancy and twin rates for 121 women who chose single blastocyst transfer and 285 women who chose two blastocyst transfer. Finds equivalent pregnancy rates for both groups (after the subsequent replacement of an additional frozen thawed blastocyst), but with only 7% twin pregnancies in the first group compared with 34% in the double transfer group. There were also 5 perinatal deaths following twin pregnancies after double blastocyst transfer.

Huddy, CLJ. Educational and behavioural problems in babies of 32 – 35 weeks gestation *Arch Dis Child Fetal Neonatal* Ed 2001; 85: F 23 – 28

Another EPICure follow-up study finding that even for children born after 32 weeks of gestation, when ‘neurologically intact’ survival is good, educational and behavioural problems occur in 1 in 3 children at the age of 7. This type of morbidity is far more common than overt disability, and 1 in 4 children born between 32 and 35 weeks require support from non-teaching assistants at school.

Hyden-Granskog, C et al. Single embryo transfer is an option in frozen embryo transfer *Human Reproduction* 2005;

Study ran from 1998 to 2003, and showed that in all SET cryocycles (elective and non-elective) the pregnancy rate was lower than that of the DET, however when looking at just the eSET the pregnancy rate was higher.

Källén, B et al. *In vitro* fertilization in Sweden: child morbidity including cancer risk *Fertility and Sterility* 2005; 84: 605 – 610

National register study in Sweden comparing health outcomes for IVF (including ICSI) infants with all infants born. Finds higher risk of long-term morbidity, which can largely be explained by an excess of preterm and multiple births, but which might also mirror different parental attitudes toward medical care for their children.

Källén, B et al. *In vitro* fertilization (IVF) in Sweden: infant outcome after different IVF fertilization methods *Fertility and Sterility* 2005; 84: 611 – 61

A national register study in Sweden, comparing the health outcomes for infants born after different IVF

techniques (standard IVF, frozen IVF, ICSI). Finds little differences between children born after different IVF techniques. The twinning rate is highest after standard IVF.

Källén, B et al. Temporal trends in multiple births after *in vitro* fertilisation in Sweden, 1982 – 2001: a register study *BMJ* 2006; 331: 382

Retrospective birth registers study analysing the incidence of multiple births after IVF in Sweden, finding a marked decrease since a 2 embryo transfer policy was introduced in the early 1990s, leading to a 70% reduction of preterm births.

Klock, SC. Psychosocial adjustment to twins after infertility *Best Practice and Research Clinical Obstetrics and Gynaecology* 2004; 18: 645 – 656

Review article of the available data on psychosocial outcomes for mothers of twins, particularly after fertility treatment. Finds that around 10% of mothers of twins experience depression, and that marital adjustment declines, particularly for first-time parents of twins.

Kurinczuk, JJ. Epidemiology of multiple pregnancy: changing effects of assisted conception in: *Multiple pregnancy* Kilby, M et al. (eds) RCOG 2006

Overview article analysing historically and geographically varying twinning rates and identifying ARTs as the major contributing factor to rising multiple rates. Also investigating mortality figures for twins and singletons. Finds that mortality rates for twins are 4 to 5 times higher than for singletons.

Kurinczuk, J et al. Methodological considerations when designing studies to examine the health of children born following ART in: Sutcliffe, AG (ed.) *Health and welfare of ART children* informa healthcare 2006

Chapter discussing the issues that should be considered when designing studies to investigate the health outcomes of children born following assisted reproductive technology conception.

Land, JA and Evers, JLH. Risks and complications in assisted reproduction techniques: Report of an ESHRE consensus meeting *Human Reproduction* 2003; 18: 455 – 457

Report of an ESHRE consensus meeting on risks and complications in ART, focussing on four topics: multiple pregnancies, long-term effects of ART on women, effects of ART on offspring, and morbidity/mortality registries. It was agreed that the essential aim of IVF/ICSI is the birth of one single healthy child, with a twin pregnancy being regarded as a complication. Recommends eSET for good prognosis patients.

Langhoff-Ross, J et al. Spontaneous preterm delivery in primiparous women at low risk in Denmark: population based study *BMJ* ; 332: 937 – 939

Study analysing the incidence of pre-term deliveries in Denmark between 1995 and 2004. Findings include substantial increase in preterm deliveries. This is partly attributed to fertility treatments with their associated high incidence of multiple pregnancies.

Ledger, WL. The cost to the NHS of multiple births after IVF treatment in the UK *British Journal of Obstetrics and Gynaecology* 2006; 113: 21 – 25

Study investigating the costs incurred to the NHS by the multiple births after IVF between 01.04.2000 and 31.03.2001. Finds that total direct costs to the NHS per IVF twin or triplet family are substantially higher than per IVF singleton. Multiple pregnancies are associated with 56% of the direct cost of IVF pregnancies, although they represent less than one third of all IVF births.

Lee, T-H et al. Embryo quality is more important for younger women whereas age is more important for older women with regard to in vitro fertilization outcome and multiple pregnancy *Fertility and Sterility* 2006; 86: 64 – 69

Retrospective record analysis of 301 patients undergoing IVF/ICSI, determining the efficiency of

embryo scoring systems for predicting conception and multiple pregnancy rates. Finds that for younger patients (≤ 35 years) the quality of the best three embryos was a determining factor, whereas for older patients (> 35 years) it was age that was more correlated with outcome.

Lesourd, F et al. Clinical and biological parameters influencing implantation: score to determine number of embryos to transfer *Reproductive Biomedicine Online* 2006; 12: 453 – 459
Single centre French study that retrospectively (739 cases) developed a clinical and embryo scoring method aimed at predicting implantation rates and then validated it prospectively to 521 cases. Factors determining the implantation rate were found to be: age, basal FSH, ovarian response, number of follicles collected, number of embryos created embryo morphology. No significant difference in implantation rates between different attempts was found. The score ended up accurately predicting the likelihood of successful treatment, but still led to a high multiple pregnancy rate.

Lukassen, HGM et al. Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial *Human Reproduction* 2005; 20: 702 – 708
Dutch health economic study assessing the cost effectiveness of two SET cycles versus one DET cycle on the basis of a study sample of 108 women (randomised controlled trial). The women were undergoing their first IVF cycle, were under 35 years old, with a basal HSG level $< 10\text{IU/l}$, and had at least two embryos available, with one excellent or one good quality embryo. The quality of the embryo was judged on the basis of fragmentation. Finds that two fresh cycles of SET are equally effective as one DET (41% versus 36% ongoing pregnancy rate), but that there are no twin pregnancies in the SET versus 37% twin pregnancies in the DET branch of the trial. Taking into account the higher costs of caring for premature and low birth weight twins, the medical costs per live birth up to 6 weeks after delivery are the same for both groups. However, if lifetime costs for severe handicap are included in the modelling, more than €7000 will be saved per live birth after SET.

Marlow, N. Does neonatal and infant neurodevelopment of twins and singletons differ? in: *Multiple Pregnancy* Kilby M et al (eds) RCOG 2006
Overview chapter analysing the cognitive differences between twins and singletons. Finds that twins are significantly more likely to be affected by cognitive developmental problems. Also finds that the differences can be explained through prematurity and low birthweight, rather than by any factors inherent to the twinning process. Also highlights the differences in the environment that twins grow up with, with more exhausted, less attentive and responsive parents.

Martikainen, H et al. One versus two embryo transfer after IVF and ICSI: a randomised study *Human Reproduction* 2001; 16: 1900 – 1903
A randomised controlled study (between eSET and DET) on women of all ages who had at least 4 good quality embryos and no more than one failed treatment cycle. The treatment outcomes including those after frozen embryo transfer were compared between the two groups. The clinical pregnancy rate per transfer was 32.4% in the eSET group and 47.1 in the DET, the difference being not significant. The cumulative clinical pregnancy rate after transfer of both fresh and frozen embryos was 47.3% in the one embryo transfer group and 58% in the two embryo transfer group. The study predicts that 20% more cycles would be needed in order to achieve the same number of pregnancies through eSET in a selected group of patients. Authors suggest that one embryo should be transferred in the first treatment cycle to women younger than 36 years who have good quality embryos; 4-cell stage on day 2 or 8-cell stage on day 3 after fertilisation, equal-sized blastomeres and $< 20\%$ fragmentation.

Murray, S et al. A randomized comparison of alternative methods of information provision on the acceptability of elective single embryo transfer *Human Reproduction* 2004; 19: 911 – 916
Study assessing the effects of alternative ways of providing information about the risks of twins on 200 couples' perception of eSET. The study found that additional information and counselling did not

significantly change the couples' views on eSET, but that a fixed charge for all fresh and frozen embryo transfers following a single oocyte retrieval would lead to significantly increased acceptance of eSET policies. The perceived pregnancy rate after DET or SET was the other determining factor for couples' attitudes.

National Perinatal Epidemiology Unit (2005) A survey of current neonatal unit organisation and policy National survey commissioned by the Baby Charity Bliss which finds that many neonatal units routinely care for more babies in special care, high dependency and intensive care than they have the facilities and staffing to support. The shortfall in recommended nurse staffing levels was marked, with only three of the 143 units for which data are available achieving the commended establishment. The staff and bed shortages mean that many babies, at least three a day, are transported outside of their own care network into hospitals, the average length of the journey is 126 miles.

Nelson HB and Martin CA. Increased child abuse in twins *Child Abuse and Neglect* 1985; 9: 501 – 505 The analysis of a US register for abuse and at-risk children found that twins were significantly over-represented, with premature birth neonatal complications, isolation, financial pressures, exhaustion and increased family size all being risk factors.

Oakley, L and Doyle P Predicting the impact of in vitro fertilisation and other forms of assisted conception on perinatal and infant mortality in England and Wales: examining the role of multiplicity *BJOG* 2006; 113: 738 – 741

Using mortality statistics and estimates of the proportion of births following infertility treatment, the authors investigate the contribution of multiple births after ART to perinatal mortality. They estimate that in 2001 73 perinatal deaths could have been avoided had all IVF infants been born as singletons or as spontaneously occurring monozygotic twins. Including all types of assisted conception (including IUI), they estimate that more than 220 perinatal deaths are attributable to the excess risks of multiple pregnancy and birth

Olivennes, F. Double trouble: yes a twin pregnancy is an adverse outcome *Human Reproduction* 2000; 15: 1662 – 1665

Summary report of all the factors that lead to higher maternal morbidity and mortality and worse perinatal outcomes for multiple pregnancies. Reports French data according to which the prematurity rate (< 37 weeks) was almost 40% in twins versus 4.5% in singletons. Almost one third (31.5%) of very premature births (< 33 weeks) were related to ovarian stimulation.

Olivennes, F et al Behavioural and cognitive development as well as family functioning of twins conceived by assisted reproduction: findings from a large population study. *Fertility and Sterility* 2005; 84:725-733

A large French population study, comparing parents of IVF twins and singletons, finds that there are no significant differences in child behaviour between the children (apart from cognitive development where twins showed significantly lower levels) but that parents of twins report greater difficulties in parenting and more problems with child behaviour.

Ombelet W et al. Perinatal outcome of 12021 singleton and 3108 twin births after on-IVF-assisted reproduction: a cohort study *Human Reproduction* 2006; 21: 1025 – 1032

Belgian retrospective study based on data from the regional Flemish registry of all hospital deliveries during the period from January 1993 – until December 2003 to investigate differences in perinatal outcome of singleton and twin pregnancies. ART singletons and twins showed significantly higher incidence of prematurity and low-birth weight, with multiple pregnancy being the biggest risk factor for ART conceived children.

Pandian, Z et al. Number of embryos for transfer after IVF and ICSI: A Cochrane review *Human*

Reproduction 2005; 20: 2681 – 2687

The four existing randomised controlled trials on SET versus DET were reviewed under Cochrane Collaboration review methods. DET leads to a higher live birth rate per woman in a fresh IVF cycle, but comparable results are obtained by subsequent transfer of a frozen embryo. The multiple pregnancy rate is significantly higher after DET.

Pennings, G. Avoiding multiple pregnancies in ART – Multiple pregnancies: a test case for the moral quality of medically assisted reproduction *Human Reproduction* 2000; 15: 2466 – 9
Opinion article discussing multiple pregnancies as a test case for the moral quality of medical practices in ART. Holds that known negative outcomes of ART are the responsibility of the clinician and that multi-fetal pregnancy reduction is only an acceptable solution to the risks of multiple birth if the physician has taken all reasonable steps to prevent the occurrence of a multiple pregnancy in the first place.

Pennings, G. Legal harmonization and reproductive tourism in Europe *Human Reproduction* 2004; 19: 2689 – 269

Opinion article arguing that increased European integration and harmonisation of legislation on assisted reproductive technologies might not be unambiguously desirable, because it would necessary ignore the existing moral and social pluralism of all European societies. Instead holds that people's decision to travel abroad into legislative systems that allow them to partake in the desired treatment is an expression of their moral autonomy.

Petrou, S et al. The long-term costs of preterm birth and low birth weight: results of a systematic review *Child: Care, Health and Development* 2001; 27: 97 -115

Systematic review of the evidence regarding the long-term economic implications of preterm birth and low birth weight, including special education, social services and families and carers.

Pinborg, A. IVF/ICSI twin pregnancies: risks and prevention *Human Reproduction Update* 2005; 11: 575 – 593

Systematic review of all the available English language literature since 1978 regarding short- and long-term outcomes of IVF and ICSI twin pregnancies. Concludes that the 'considerable higher risk of adverse obstetric outcome in IVF twins than in singletons and the 20fold higher ART twin birth rate is still one of, if not, the most serious adverse effect of ART.

Pinborg, A et al. Attitudes of IVF/ICSI-twin mothers towards twins and single embryo transfer *Human Reproduction* 2003; 18: 621 – 627

Danish study assessing women's views on eSET who had 3 to 4 year old twins after IVF, mothers of naturally conceived twins and mothers of IVF singleton babies (1769 mothers in total). Many mothers of twins still were not convinced of the need for eSET. However, the study found that having had a child with very low birth-weight was highly predictive of an acceptance of eSET, highlighting the fact that only parents who have experienced the stress of twins who were unwell at birth take the risk of multiple births seriously enough to determine their treatment preference.

Pinborg, A et al. Morbidity in a Danish National cohort of 472 IVF/ICSI twins, 1132 non-IVF/ICSI twins and 634 IVF/ICSI singletons: health-related and social implications for the children and their families *Human Reproduction* 2003; 18: 1234 – 1243

Large national cohort study finding no major differences in physical health between IVF twins and non IVF twins. Finds that compared to IVF singletons more IVF twins were admitted to a neonatal intensive care unit and more had surgical interventions, special needs and poorer speech development. The discrepancies could be entirely explained through prematurity and low-birthweight of the twins. Also shows that twins parents experience more marital stress and that twins have more impact on the mother's life.

Schimmel, MS et al. Very low-birth-weight-infants conceived by in vitro fertilization are not at higher risk for mortality and morbidity: a population-based study *Fertility and Sterility*; 85: 907 – 912
Israeli population-based observational study from 1995 – 2002 that compared IVF very-low-birth-weight babies (vlbw) with naturally conceived vlbw babies and found no excess mortality or morbidity in the IVF babies. Approximately 40% of the twins and 86% of the triplets were conceived by IVF, which has led to an increase in perinatal morbidity and mortality in Israel. Conclusion: IVF per se is not a risk factor for babies, prematurity after multiple pregnancy is the main factor leading to adverse outcomes of infants conceived by IVF.

Sebire, NJ. Anomalous development in twins (including monozygotic duplication) in: *Multiple Pregnancy* Kilby M et al (eds), RCOG 2006

Overview chapter analysing the available data on congenital abnormalities in twins, concludes that the risks are clearly increased for monozygotic and monochorionic twins, but that dizygotic twins probably do not have a significantly increased risk of congenital abnormalities.

Sen, D and Robson S. Effects of the birth of multiples on parents' psychological wellbeing in: *Multiple Pregnancy* Kilby M et al (eds), RCOG 2006

Overview article investigating the psychosocial outcomes for twin families, finding higher rate of exhaustion and extreme parental fatigue in families with multiples. Also finds that depression, anxiety, stress and fatigue occur more frequently and with higher intensity in parents of multiples than in parents of singletons. Also finds that families of multiples are at increased risk for marital separation and divorce. There is also concern about the substantial increased risk of physical and mental child abuse in families with multiples.

Simmons, R et al. Dramatic reduction in triplet and higher order births in England and Wales *BJOG* 2004; 111: 856 – 858

Analysis of the data provided by the Office for National Statistics showing rising number of twin births, attributable to IVF, but a marked decline of triplet and higher order births in England and Wales. Since 1998, their number dropped by one quarter. The authors probably reflects both voluntary and statutory regulation of treatment regimes.

Tang, R et al. Towards defining parameters for a successful single embryo transfer in frozen cycles *Human Reproduction*; 21: 1179 – 1183

A retrospective analysis of 891 frozen embryo cycles (FET), involving 404 sFET and 487 dFET cycles performed in one Australian centre. There was no significant difference in implantation and pregnancy rates between sFET and dFET cycles, but 1 in 5 dFET cycles led to multiple pregnancies, compared to none after sFET. Both blastomere lysis and cleavage affected the outcome in sFET. To avoid the risk of twins, sFET should be considered when the embryo shows less than 25% blastomere lysis and at least one blastomere cleaves. This necessitates the freezing and thawing of individual embryos.

Templeton A. Avoiding multiple pregnancies in ART. Replace as many embryos as you like – one at a time. *Human Reproduction* 2000; 15: 1662 – 1665

Opinion paper arguing that multiple births is the single biggest risk factor for IVF children and that under welfare of the child aspects the obvious way forward is the introduction of single embryo transfer in most cases.

Thurin, A et al. Elective single-embryo-transfer versus double embryo transfer in IVF *New England Journal of Medicine* 2004; 351: 2392 – 2402

A randomised multi-centre study comparing eSET plus frozen ET to DET in 661 patients under 36 years who had at least two good quality embryos. The pregnancy rate resulting in at least one live birth was 38.8% in the eSET plus frozen ET group and 42.9% in the DET group. The twin rate was 0.8% and

33.1% respectively. Study shows that eSET, plus if necessary frozen embryo transfer leads to a dramatic reduction of the multiple births rate without a substantial reduction in the rate of pregnancy.

Thurin, A et al. Randomized single versus double embryo transfer: obstetric and paediatric outcome and a cost-effectiveness analysis *Human Reproduction* 2006; 21: 210 – 216
Swedish multi-centre study comparing the obstetric and health outcomes (up to 6 months after birth) for children born after eSET and DET. There were markedly fewer maternal and paediatric complications in the SET group, resulting in lower overall costs for single plus frozen embryo transfer policies.

Thurin, A et al. Predictors of ongoing implantation in IVF in a good prognosis group of patients *Human Reproduction* 2005; 20: 1876 – 1880

Follow-up study to the above, investigating factors impacting on implantation rate. Finds that 4 cell embryos, first IVF cycle, IVF as a fertilisation method and ovarian sensitivity were predictors of good implantation and ongoing pregnancy rates, whereas ICSI, non-4-cell embryos and previous failed IVF cycle were predictors of lower implantation rates.

Tiitinen, A et al. Elective single embryo transfer: the value of cryopreservation *Human Reproduction* 2001; 16: 1140 – 1144

Follow-up study to an earlier eSET trial, reporting cumulative pregnancy rates after additional frozen/thawed cycles. The patients who initially received only one embryo have a cumulative pregnancy rate of 52.8% with a twin rate of 7.6%. Concludes that eSET with a good cryopreservation programme results in very acceptable pregnancy rates with a low risk of twins.

Van Montfoort, APA et al. In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial *Human Reproduction* 2006; 21: 338 – 343

A randomised controlled trial of around 300 patients in one Dutch centre finding that applying eSET to all patients would eliminate twinning, but would also almost halve the pregnancy rate (from around 40% to around 20%). The pregnancy rate after eSET in a selected group of good prognosis patients was found to be not significantly different from DET success rates (33% vs 30%), but the twinning rate remained relatively high at 12.9%.

Van Monfoort, APA et al. Elective single embryo transfer (eSET) policy in first three IVF/ICSI treatment cycles *Human Reproduction* 2005; 2: 433 – 436

eSET can be performed in a select group of patients (younger than 38, with at least one good quality embryo) can be performed in the first, second and third cycles whilst maintaining a pregnancy rate comparable to DET.

Veleva, Z et al. Elective single embryo transfer in women aged 36 – 39 years *Human Reproduction* 2006; 21: 2098 – 210

Retrospective analysis of more than 2000 cycles in women aged 26 – 39, comparing DET and eSET pregnancy and multiple rates. Finds no significant difference in pregnancy rate per embryo transfer and live birth rate, but finds a higher cumulative pregnancy rate (combining fresh and frozen cycles) after eSET than after DET. Also finds much lower multiple rate for eSET group (1.7% compared to 16.6%).

Verstraelen, H et al. Preterm birth in twins after subfertility treatment: population based cohort study *BMJ* 2005; 331: 1173 – 1177

Belgian Population based cohort study assessing gestational length and prevalence of preterm birth among medically and naturally conceived twins. Conclusions: Twins resulting from subfertility treatment have an increased risk of preterm birth, but the risk is limited to mild preterm birth, primarily by virtue of dizygotic twinning. Reports that “about half of medically conceived babies in the United States and

Europe are now born as twins, and almost half of all twins result from subfertility treatment”.

Wennerholm, U and Bergh, Ch. Perinatal outcome after assisted conception in: Sutcliffe, AG (ed.) *Health and welfare of ART children* informa healthcare 2006

Chapter reviewing the existing literature on health outcomes for ART children, finding that the biggest single risk factor for children born after IVF/ICSI is the increased incidence of multiple and preterm birth, but that an elimination of the risk of multiple pregnancies will not totally eliminate all the risks associated with IVF pregnancies.

Wood NS et al. Neurologic and developmental disability after extremely preterm birth *New England Journal of Medicine* 2000; 343: 378 – 384

Big multi-centre study (EPIcure) that evaluated all children born at 25 weeks or earlier between March and December 1995 when the children reached an age of 30 months. 49% of all the survivors had a disability, about half of these met the criteria for ‘severe disability’, including neuro-motor disability, loss of hearing and blindness. Preterm birth has considerable impact on long term future health: 1 in 4 survivors born at less than 25 weeks’ gestation have severe mental or physical disability.

Glossary

ACE

Association of Clinical Embryologists. It is the professional body of and for embryologists in the UK, set up to promote high standards of practice in clinical embryology and to support the professional interests of embryologists working in the UK. - www.embryologists.org.uk

All Party Parliamentary Group on Infertility

A group that raises awareness of infertility issues in Parliament and the need for full implementation of the National Institute for Health and Clinical Excellence's (NICE) clinical guidelines on the assessment and treatment for couples with fertility problems.

Anaemia

A condition characterised by too few red blood cells in the bloodstream, resulting in insufficient oxygen supply to tissues and organs.

Antenatal (prenatal) care

Care provided between conception and birth.

ART

Assisted Reproductive Technologies.

ASRM

American Society of Reproductive Medicine. A voluntary, non-for-profit organisation devoted to advancing knowledge and expertise in reproductive medicine, including infertility, menopause, contraception, and sexuality. - www.asrm.org

Assisted hatching

A technique involving the artificial creation of an opening in the outer shell of an embryo. It is used to help the growing embryo to emerge from the shell in order to implant properly in the uterus. Can be done by use of lasers, chemicals or mechanically.

Attention deficit hyperactivity disorder (ADHD)

A condition seen in children where there is an increased motor activity in association with poor attention span.

Bertarelli Foundation

A group that serves researchers, patients and practitioners in the field of infertility treatment by supporting numerous research projects and by contributing to the creation and distribution of knowledge in the field of reproductive health. - www.bertarelli.edu

BFS

British Fertility Society. A national multidisciplinary organisation representing professionals practising in the field of reproductive medicine. - www.britishfertilitysociety.org.uk

BICA

British Infertility Counselling Association. A professional organisation for fertility counsellors and counselling in the UK. It seeks to promote the highest standards of counselling for those considering or undergoing fertility investigations and treatment. - www.bica.net

Blastocyst

An embryo that has developed for five to six days after fertilisation.

Blastocyst transfer

This is performed when the embryos are cultivated for 4-5 days to approximately 64-cell stage at embryo transfer.

Blastomere

A cell taken, by biopsy, from a blastocyst.

Cell division

The separation of one cell into two daughter cells.

Cerebral cyst

A thin-walled abnormal sac or cavity in the brain, containing fluid.

Cerebral hydrocephalus

A condition in which fluid accumulates in the brain.

Cerebral palsy

A condition where parts of the brain are damaged, usually through lack of oxygen, often during the process of birth or when a premature baby cannot breathe properly, which affects the person's control over muscle movements. It is not progressive (i.e. it doesn't get worse as time goes by) and it does not necessarily affect a person's cognitive development or intelligence.

Chorionicity

Refers to the connection between the fetus and the placenta in twin pregnancies. Monochorionic twins share a placenta. Dichorionic twins each have their own placenta and gestational sac.

Cochrane review

A review by the Cochrane Collaboration, an international not-for-profit organisation providing up-to-date information about the effects of health care. It regularly reviews the available evidence on health care interventions in order to facilitate evidence-based medicine - www.cochrane.org

Code of Practice

A Code issued by the HFEA containing guidance and rules for fertility and research centres. The Code can be found on the HFEA website. - www.hfea.gov.uk

Cohort (observational) study

Study of a group of people with shared characteristics, normally after a health care intervention you wish to evaluate.

Congenital malformations

Any malformation which is noticed at birth, whether it is the result of a genetic (inherited) or environmental cause.

Cryopreservation

Preserving substances at very low temperatures in vapour-phase or liquid nitrogen at -196 degrees centigrade. E.g.: frozen sperm, embryos, eggs, testicular tissue and ovarian tissue.

Culturing in vitro

Developing outside the body (i.e. in the laboratory).

Cumulative or fresh/frozen pregnancy rates

Pregnancy rates that are added up after all the eggs collected during the initial stimulated cycle have been used up, including those that were initially frozen.

DET

Double Embryo Transfer. Transferring two embryos at the same time to a woman undergoing IVF.

Dichorionic twins

Twins that each have their own placenta and gestational sac.

Dizygotic twins (non-identical twins)

Dizygotic twins form when two separate eggs are fertilised by separate sperm (two zygotes). These twins are no more alike than any other brothers or sisters.

Egg collection

Procedure by which eggs are collected from the woman's ovaries by using an ultrasound guided needle, or by using a laparoscope (an instrument used for looking into the abdomen) and a needle. Also known as egg retrieval.

Embryo grading systems

Systems used to rate embryos so that only the embryos with the highest chance of implantation are chosen for transfer or freezing.

Embryo morphology

The configuration of the embryo, used to judge the quality of the embryo (its potential to implant or survive freezing).

Embryo score

See embryo grading.

eSET

Elective Single Embryo Transfer. The principal way in which multiple births after IVF can be reduced, by only transferring one embryo at a time to the woman's womb.

ESHRE

European Society for Human Reproduction and Embryology. The main aim of the ESHRE is to promote interest in, and understanding of, reproductive biology and medicine. - www.eshre.com

EU Tissue Directive

The EU Tissues and Cells Directive sets standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissue and cells intended for human application. It was adopted by the European Parliament on 7th April 2004.

Fertility Friends

Fertility Friends is an online meeting place for couples in the UK since 2002. Its aim is to help people through the difficult process of assisted conception by sharing thoughts, experiences and knowledge with others. - www.fertilityfriends.co.uk

Fetal reduction

Also called multi-fetal pregnancy reduction or selective abortion, where one or more of the fetuses is aborted in order to achieve a singleton or lower order multiple birth.

Fetus

Middle stage of development between the embryonic stage and the birth of the baby, when all main recognisable features are shown, i.e. from the end of the second month of pregnancy.

Fragmentation

When parts of the cells comprising the embryo spontaneously break off. Embryos with high levels of fragmentation are considered poor quality.

Fresh cycle

An IVF cycle using fresh (not previously frozen) embryos for transfer.

Frozen or thawed cycle

An IVF cycle using embryos that were frozen after creation and then thawed for transfer.

FSH units

Follicle stimulating hormone units. Refers to the amount of drugs a woman needs to receive in order to generate eggs for collection.

Genes

Parts of the chromosomes that control the inheritance of hereditary characteristics e.g. hair and eye colour.

Gestational age

Fetal age of a newborn, calculated from the number of completed weeks since the first day of the mother's last menstrual period to the date of birth.

Gestational diabetes

A glucose intolerance which occurs in pregnancy, usually noticed between the 24th and 28th weeks of pregnancy. In most cases the blood glucose level returns to normal after delivery. Although the symptoms of this form of diabetes are mild and non-serious for the mother, elevated blood glucose in the mother has been associated with an increased risk of foetal and newborn death. Risk factors for gestational diabetes include maternal age over 25, family history of diabetes, obesity, birth weight over 9 lb in a previous delivery and multiple pregnancy.

Gestational weight

The weight of a newborn at gestational age.

Glucose intolerance

Glucose is the simple sugar that the body obtains from food. Insulin is a hormone produced by the pancreas to help the body's cells use the glucose for energy. When there is insufficient insulin, or when the body is unable to use the insulin that is manufactured, an excess of glucose builds up in the blood, which results in elevated blood glucose (or blood sugar) levels.

Haemorrhage

Bleeding.

HFE Act

The Human Fertilisation and Embryology Act 1990.

HFEA

Human Fertilisation and Embryology Authority. The HFEA's primary remit is to license and monitor UK clinics that offer IVF (*in vitro* fertilisation) and DI (donor insemination) treatments, and all UK-based research with human embryos. It also regulates the storage of eggs, sperm and embryos. - www.hfea.gov.uk

HFEA register

A confidential register of information about donors, patients and treatments provided by HFEA licensed treatment centres. It was set up in 1991 and it contains information concerning children conceived from licensed treatments from that date onwards.

HFEA's patient panel

A group of previous or current IVF patients who help the HFEA with its policy development by giving their views and commenting on proposals. Anyone undergoing or considering fertility treatments can join it. www.hfea.gov.uk

Higher order pregnancies

A pregnancy with three or more fetuses. These pregnancies can arise from one, two or more fertilised eggs implanted in the uterus and developing into babies.

Hypertension

Persistently high arterial blood pressure. Hypertension may have no known cause or be associated with other primary diseases or conditions and is one of the most common risks of pregnancy.

Iatrogenic multiple births

Medically induced multiple births.

ICSI

Intra-Cytoplasmic Sperm Injection. Process in which a single sperm is inserted directly into the egg, thus bypassing all natural barriers a sperm has to encounter. This technique is usually used when there is a low sperm count or reduced sperm motility.

Implantation

The embedding of a fertilised ovum in the uterus.

IQ

The intelligence quotient. A numerical scale that attempts to measure the intelligence of an individual, usually based on the results of a written test.

IUI

Intra-Uterine Insemination. Injection of sperm into the uterus of a woman

IVF

In Vitro Fertilisation. The mixing of human eggs and sperm in a laboratory to achieve fertilisation outside the body.

Licence Committee

An HFEA committee that ensures compliance of licensed centres with HFEA guidance.

MFPR

Multifetal Pregnancy Reduction. See: fetal reduction.

Miscarriage

The loss of a pregnancy before the fetus is 24 weeks old.

Monochorionic twins

Twins sharing a gestational sac and placenta. This bears higher risks for the fetuses during pregnancy and birth. It can only occur in identical twins because they develop out of the same egg, part of which develops to form the placenta.

Monozygotic twins

Twins who are derived from a single egg (zygote). Monozygotic twins form when one fertilised ovum separates into two identical zygotes.

Morbidity

A state of disease.

Mortality

Death. The risk of mortality refers to the number of patients who die after a medical intervention or event.

Natural cycle IVF

IVF without ovarian stimulation. Rather than collecting numerous eggs and creating a number of embryos, the one naturally maturing egg is collected and fertilised for transfer.

Neonatal intensive care

Intensive care for newborn babies.

NIAC

National Infertility Awareness Campaign. Campaign led by IN UK (Infertility Network UK) primarily aimed at implementation of the NICE fertility guideline. - www.infertilitynetworkuk.com

NICE

National Institute for Health and Clinical Excellence. A special health authority which was set up by statutory instrument in 1999 to make resource allocation decisions in the NHS more explicit and transparent, and to address the problem of the 'postcode lottery'. - www.nice.org.uk

NICE guidelines

Guidelines issued by the National Institute for Health and Clinical Excellence.

Obstetric care

The care of women during pregnancy, childbirth, and the period during which they recover from childbirth.

Oocyte

The female gamete (egg).

Operative delivery

Expulsion or extraction of the child and the after-birth involving surgery.

Ovary

The female reproductive organ producing oocytes (eggs).

Ovarian sensitivity

The number of eggs retrieved in relation to the total number of FSH units (see above) administered.

Ovarian stimulation

Stimulation of the ovaries with drugs in order to retrieve multiple eggs.

Oxygen dependence

Describes patients who are not strong enough to breath sufficiently themselves and are therefore dependent on the artificial input of oxygen.

Paediatric services

Medical services relating to the care and medical treatment of children.

PCT

Primary Care Trust. Regional NHS bodies that are responsible for commissioning (ordering and buying) NHS services locally.

Perinatal care

The care and management for newborn babies, up to 7 days after the day of delivery.

Perinatal death

stillbirths and deaths up to 7 days post-partum.

Placenta

The organ in the womb that provides the fetus with nutrition and oxygen during the pregnancy.

Pre-eclampsia

A disorder that occurs during pregnancy and the postpartum period and affects both the mother and the unborn baby. Affecting at least 5-8% of all pregnancies, it is a rapidly progressive condition characterised by high blood pressure and the presence of protein in the urine. Pre-eclampsia and other hypertensive disorders of pregnancy are a leading global cause of maternal and infant illness and death.

Pre-implantation biopsy

The taking of one or two cells from an embryo before transfer to the woman's uterus for laboratory examination. Used in the context of PGD/PGS.

Pre-implantation Genetic Diagnosis (PGD)

A screening process in which one or two cells from an embryo are removed, to test for a specific inherited disease.

Preimplantation genetic screening for aneuploidy (PGS)

A screening process in which one or two cells from an embryo are removed, to test that they contain the correct number of chromosomes and not more or less than usual (aneuploidy). Only normal appearing embryos will be selected for transfer.

Prematurity

The current World Health Organisation definition of prematurity is a baby born before 37 weeks of gestation, counting from the first day of the last menstrual period.

Pre-term labour

Labour prior to 37 weeks of gestational age.

Randomisation

The process by which patients in a clinical trial are randomly assigned to different treatments. Randomisation minimises the differences among groups by equally distributing people with particular characteristics among all the trial arms. It is considered the best way to assess the efficacy of a given medical treatment.

Randomised controlled trial (RCT)

In a RCT, the research participants are randomly allocated, usually by computer, to either the control or the active arm of the study. Those in the active arm are given the new treatment, while those in the control group are given either an inert placebo or the current best available treatment. Researchers will be interested in whether more of the patients in the active arm are showing signs of improvement than in the control group. RCTs are considered to be the 'gold standard' in medical research.

RCOG

Royal College of Obstetricians and Gynaecologists. The RCOG is dedicated to the encouragement of the study and the advancement of the science and practice of obstetrics and gynaecology. - www.rcog.org.uk

RCPCH

Royal College of Paediatrics and Child Health. The main objects of the College are to advance the art and science of paediatrics, improve standards of medical care to children, and to educate and examine doctors in paediatrics. Additionally, the College has a function in providing information to the public on the healthcare of children www.rcpch.ac.uk

Reproductive tourism

Term that refers to people going abroad for fertility treatment rather than accepting the treatment choices available in the UK.

ROP

Retinopathy of Prematurity. A serious eye problem that can affect premature babies.

Selective abortion (multifetal pregnancy abortion)

Abortion in order to achieve a singleton or a lower order multiple birth.

Significance

A statistical concept which means that although differences in outcomes might have been measured, they were not clear enough to be certain that they were not simply due to chance. The smaller a study is, the less confident you can be that findings are significant in this sense of the word.

Singleton pregnancy

A pregnancy with only one fetus.

Soft IVF

IVF whereby the woman's ovaries are only stimulated to produce a small number of eggs, or only one egg, rather than the high numbers normally aimed for in IVF that is based on embryo selection and freezing.

Spontaneous multiple pregnancy

Pregnancy with two or more fetuses after natural conception.

Thromboembolism

Obstruction of a blood vessel by a blood clot carried by the blood stream.

Twin-to-twin transfusion syndrome

Syndrome caused by the fact that fetuses share the placenta unequally, which leads to imbalanced circulation between the placenta and the fetuses.

Two-pronuclear stage

An egg in the process of fertilisation, before the nuclei of the egg and sperm (pronuclei) have fused.

Uterus

A small, hollow, muscular organ found in the female pelvis that carries the fertilised ovum through the nine months of pregnancy, enlarging to accommodate the fetus as it grows.

Zygote

A fertilised egg.

