Avoiding multiple pregnancies in in-vitro fertilization: who’s afraid of single embryo transfer?

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Multiple pregnancy rates in most in-vitro fertilization (IVF) programmes are still ~30% despite technological developments in assisted reproduction. This is because we still have to use an imprecise and risky strategy to achieve acceptable pregnancy rates: that is to replace more than one embryo.

In the debate on embryo transfer and multiple gestation in Human Reproduction (Bronson et al., 1997), most contributors stressed the need for further research into laboratory aspects reflecting embryo quality, such as prolonged in-vitro culture, embryo co-culture techniques, or embryo biopsy. They stated that only new developments in these areas would produce a scientific basis robust enough to justify the elective transfer of one single embryo in IVF. This is rather a fatalistic view that ignores the possibility of further reducing the number of embryos per transfer, even with our current knowledge of embryo implantation.

Most fertility workers reject the idea of replacing only one embryo because they fear it will reduce success rates. Nevertheless, every fertility worker has dealt with young patients with a twin pregnancy after transfer of two good quality embryos during a first treatment cycle, in which it would have been better to transfer a single embryo. In other words, even though transfer of one embryo in every patient would certainly cause a dramatic fall in overall pregnancy rates, a specific subgroup of patients at risk for multiple gestation would benefit from this, even with current IVF techniques.

We therefore need to consider an individualized embryo transfer policy: elective transfer of a single embryo in patients at risk for multiple gestation and a more liberal attitude for those with a less good prognosis. Would this reduce significantly the number of multiple pregnancies without dramatic fall in overall success rates? Can we in fact anticipate the effect of such a strategy on our IVF results, in terms of the overall pregnancy rate and multiple pregnancy rate? We tried to do so using data from our own IVF/intracytoplasmic sperm injection (ICSI) programme and would encourage other centres to apply a similar rationale to their data.

Rationale for single embryo transfer: what can be anticipated?

Analysing the results of 2771 IVF or ICSI cycles, the following factors associated with a good prognosis were singled out: age <36 years; first, second, or third IVF or ICSI cycle; more than three embryos available for transfer; transferred embryos of good quality (scoring at least 4 on a scale of 1–5). In 733 of 2771 IVF or ICSI cycles (26%), the above-mentioned criteria associated with a good prognosis were met. In this group, 325 intrauterine clinical pregnancies were achieved (44%/cycle). Of these, 216 were singleton pregnancies (67%), 94 were twins (29%) and 15 triplets (5%). The replacement of 1710 embryos led to 449 gestational sacs (clinical intrauterine implantation rate per transferred embryo of 26%). Out of 2771 IVF or ICSI cycles, 841 led to an intrauterine clinical pregnancy (30%/cycle), of which 606 were singletons (72%), 202 were twins (24%), 32 triplets (4%) and one quadruplet (<1%). Therefore, 26% of the cycles accounted for 46% of the multiple pregnancies (109/235).

If single embryo transfer had been performed in this good prognosis subgroup, 191 clinical pregnancies instead of 325 would have been obtained (given the implantation rate of 26% per embryo), and 733 embryos would have been transferred to obtain these 191 pregnancies. An extra 977 extra spare embryos would have been left in frozen storage. Given a frozen–thawed embryo survival rate of 50% and a clinical implantation rate per transferred thawed embryo of at least 5%, thawing and transfer of the extra spare embryos would have resulted in 23 more pregnancies. This would have brought the total number of clinical pregnancies obtained by elective single embryo transfer in the good prognosis subgroup to 214. To compensate for the 111 missed clinical pregnancies and given the pregnancy rate per elective single embryo transfer of 26%, 427 extra cycles (427/2771, or 15%) with single embryo transfer would have had to be performed. All these extra pregnancies would of course have been singletons.

Overall, from the total number of 841 clinical pregnancies, 715 would have been singletons (85%), 108 twins (13%), 17 triplets (2%) and one quadruplet (<1%). The number of multiple pregnancies overall would have been 126 instead of 235, which is a reduction of 46%. A reduction in overall clinical pregnancy rate from 30 to 26% per cycle would have been compensated for by a drop in multiple pregnancies from 28 to 15% of the total pregnancies. From Figure 1, it is clear that the reduction of the overall pregnancy rate is exclusively due to a reduction in the number of multiples. Overall, 15% extra treatment cycles would have been necessary to obtain the same total number of clinical pregnancies.

These calculations were repeated using different criteria for good prognosis. The larger the subgroup became with good prognosis, the more multiple pregnancies would have been
avoided by elective single embryo transfer, but the greater the impact would have been on the overall pregnancy rate. Therefore, the selection of the patients to receive one embryo should be made in order to keep a balance between reduction in multiple gestation and effect on overall pregnancy rate. There is no simple formula to determine the best level for this balance; how many multiple pregnancies should be avoided in order to justify a 5% reduction in overall pregnancy rate?. This is indeed a matter of clinical judgement. Therefore, the criteria used to select patients with good prognosis are not merely the result of multivariate analysis. In fact, they are also based on what is clinically judged to be best in terms of avoidance of multiple pregnancy and reduction in overall pregnancy rate with elective single embryo transfer. There will always be a price to be paid in order to avoid multiple pregnancies, but this price can be determined beforehand using specific selection criteria for the population in which only one embryo is transferred. Indeed, as Walters (1994, 1996) stated: ‘increasing or decreasing the number of replacements per transfer in IVF has an effect which can be modelled successfully in probabilistic terms’.

**Implications for future research and routine clinical practice**

Increasing the number of transferred embryos in patients with less good prognosis is accepted by most infertility centres as a routine procedure and several studies have been published on this subject (Azem et al., 1995; Adonakis et al., 1997). This is not the case for the reduction to one single embryo per transfer in patients with good prognosis, although the rationale behind this policy is exactly the same.

We think that single embryo transfer is worth consideration in patients with a good prognosis. Even with the imperfect embryo selection criteria used currently, such a strategy would probably reduce the overall incidence of multiple pregnancy by half without a dramatic fall in the success rate. Although most infertile couples are happy to accept the risk of a twin pregnancy, IVF centres should not ignore the perinatal risks and the familial impact of a multiple pregnancy. The long-term welfare of the family should take precedence over the short term goal of achieving a pregnancy and ambiguous preoccupation with success figures.

Over the past few years, we have gradually reduced the mean number of embryos per transfer from four to two and have had no difficulty in convincing our patients of the validity of this strategy in terms of the cost/benefit ratio. A further reduction to one single embryo per transfer in good prognosis cases will be similarly acceptable to patients, provided objective information is given on the increased obstetric and neonatal risk and the added socio-familial burden of twin pregnancies. It is in fact not the patients, but the IVF centres which remain to be convinced. As a first step, other centres should repeat the calculations above on their set of data, in order to prove the reproducibility of our findings in their setting. We already took the liberty of applying our rationale to published data from another IVF programme, and came to similar conclusions (Coetsier and Dhont, 1998).

We admit that a rationale based on anticipated implantation rates from retrospective data will always be somewhat speculative, but at least it represents a sound basis for prospective studies to confirm our thesis. In fact, the results of a prospective study will probably be even more spectacular, since in the retrospective study elective single embryo transfer, implantation rates were calculated as the mean implantation rate of an embryo in double or triple transfers. In a prospective setting, when the best embryo can be selected for transfer, implantation rates for elective single embryo transfer will even be higher, so that the negative effect on overall pregnancy rate will be lower. The results of such prospective studies will provide us instantly with a readily applicable guideline to avoid multiple pregnancy in IVF, even without any further research on embryo implantation.

The medical profession at large and societies for reproductive medicine in particular could help to promote this policy by stressing that the professional competence of an IVF centre should also be measured in terms of ongoing singleton pregnancies per cycle.

**References**


**An embryo too many?**

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According to the Human Fertilisation and Embryology Authority (HFEA, 1997a), the live birth rate for each cycle of in-
vitro fertilization (IVF) commenced in the UK has increased from 8.6% in 1985 to 15.0% in 1996. In spite of concern expressed by the HFEA about the incidence of multiple births, three embryos were replaced in 54.9% of the 30 354 cycles of IVF reported between January 1995 and March 1996. The clinical pregnancy rate is increased if more than one embryo is replaced. The pregnancy rate per cycle was 8.4% (278 out of 3306) after replacing a single embryo, 20.2% (2097 out of 10376) after two embryos and 26.6% (4346 out of 16672) after three embryos. The replacement of two and three embryos is associated with a significantly increased risk of a multiple birth. The chance of a triplet or quadruple pregnancy is almost 6.0% after the replacement of three embryos (Table I).

**Perinatal mortality and IVF treatment**

The perinatal mortality rate (PMR) for IVF pregnancies in 1995 was 22.6 out of 1000 (HFEA, 1997a). The PMR in England and Wales during the same interval was 8.7 out of 1000. This is similar to that seen with IVF single births. The rate rises to 46.8 out of 1000 with IVF twins and 82.6 out of 1000 for IVF triplets (Table II).

The increase in the perinatal mortality rate following IVF treatment is likely to be due to the increased incidence of preterm birth associated with multiple pregnancies. The birth weight distribution and duration of IVF pregnancies in single and multiple births has not been reported by the HFEA. The publication of such data and the correlation with the PMR is necessary to confirm this relationship.

An adjusted live birth rate for each cycle of IVF commenced in clinics licensed by the HFEA is published in ‘The Patient's Guide to Donor Insemination and IVF Clinics’ (HFEA, 1997b). The publication of such data facilitates the compilation of ‘league tables’. These ‘league tables’ encourage purchasers of IVF services to select a clinic on the basis of the live birth rate. In all but one of the 12 clinics with IVF live birth rates of >20.0%, the multiple birth rate was >30.0% (median 32.0%, range 29–40%) and the triplet pregnancy rate was as high as 12% (median 3.0%, range 0–12%).

Mugford and Henderson (1995) estimated the health service costs for children born in single and multiple births. Neonatal care forms the largest single component of expenditure on multiple births. The average costs for babies weighing <1500 g were £8000–9000 per baby at 1994 prices. The cost was £1534 per set of twins, £6442 per set of triplets and £18 994 for a quadruplet birth. Using their estimates, the cost of hospital services for multiple births arising from IVF treatment in 1995 was £4.3 million.

Over and above the increased risk of the babies dying, the increased possibility of disability should be borne in mind (Doyle, 1996). It is known that the risk of cerebral palsy, blindness, learning and behavioural disorders is increased with the birth of premature babies. Follow-up studies in Manchester of the children conceived after IVF, have shown that the outcome of IVF treatment leading to multiple births is less satisfactory than with singleton births, because of neonatal conditions associated with pre-term delivery and disabilities in later childhood (D’Souza et al., 1997). A birth weight-specific study of multiple births in Merseyside and Cheshire has shown that ‘if both twins are live births there is a 1 in 56 probability that one has cerebral palsy and 1 in 430 that both have it’. Furthermore ‘if one of the twins is a stillbirth, there is a one in 10 probability that the other has cerebral palsy’ (Pharaoh and Cooke, 1996).

**Multiple births, the family and relationships**

To avoid the problems associated with multiple births, Coetsier and Dhont (1998) have suggested that it is worth replacing a single embryo in patients with a good prognosis. Couples often state that it would be ‘a pleasure to have twins’ and they would happily face the prospect of triplets if that meant a ‘successful outcome’. The rearing of twins and triplets is associated with particular difficulties (Garel and Blondel, 1992) and multiple pregnancies should not be considered as an IVF success (Olivennes and Frydman, 1998). Studies of families with surviving triplets have shown that maternal bonding is likely to be impaired. The mothers are often physically exhausted. After 4 months, many of the parents feel socially isolated, report marital disharmony and experience ‘domestic overload’. Some mothers avoid emotional involvement with the children because of fear of the competition amongst the siblings. The parents complain of exasperation and hostility because of continual exhaustion. There is little expert advice available. Home help often fades out after ~6 months. Treatment for major depressive illnesses and serious psychological problems is common in these mothers. These problems persist, and 4 years after delivery, mothers of triplets still report fatigue, emotional stress and difficult relationships with their children (Doyle, 1996; Garel et al., 1997).

**How many embryos should be replaced?**

All women with more than one embryo have a choice in this matter. Information in the HFEA Sixth Annual Report (1997a) is most helpful in answering this question (Table III). When
four or more embryos have been created, the live birth rate is similar to that after the replacement of two or three embryos. However, there is a 3% increase in the multiple birth rate if three embryos are replaced. Women who have four or more embryos created should seriously consider replacing two and freezing the rest. Women with only three embryos could make a decision based on their age (Templeton et al., 1996) and the success rates for the freezing and subsequent use of a single frozen embryo. Women with only two embryos could have both replaced.

**Replacing two embryos and embryo cryopreservation**

A cumulative viable pregnancy rate of 40.0% is possible (Horne et al., 1997), by using a maximum of two embryos per replacement in conjunction with a cryopreservation programme. The results in this prospective randomized study show that the chances of having a successful outcome to a course of IVF treatment are not decreased by the replacement of two embryos. Cumulative live birth rates are not published by the HFEA. To publish such information it is necessary to know the outcome in individual women of every episode of fresh and frozen embryo replacement. The information is thus limited to that group of women who reach these stages in IVF treatment.

Follow-up studies of the children born after the replacement of freeze/thawed embryos is reassuring (Sutcliffe et al., 1995a). The development of the children did not cause concern and the minor congenital anomaly and major congenital malformation rates were similar to those conceived normally (Sutcliffe et al., 1995b).

**Embryo reduction**

Faced with the prospect of a triplet pregnancy, some couples may contemplate embryo reduction from triplets to twins. The procedure increases the probability of a delivery after 32 weeks of gestation, but also increases the risk of miscarriage. The incidence of preterm delivery at 24–32 weeks is reduced from 17.5 to 4.7% (Sebire et al., 1997). This is of importance given that 38% (48 out of 125, 95% CI 30–47) of infant survivors born at 24 weeks and 24% (84/352, 95% CI 20–28) of survivors born at 26 weeks are handicapped (Rennie, 1996).

**Conclusions**

The time has come to replace a maximum of two embryos when more than three have been created. Such a policy would reduce the numbers of women having to resort to embryo reduction, as well as reducing the incidence of multiple births, particularly triplets, and fewer children would be born prematurely. The perinatal mortality rate associated with IVF conceptions would decrease as would the significant risk of disability in the survivors. Finally, the hospital expenditure associated with IVF multiple births would also decrease.

**References**


**How many embryos should be transferred?**

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This year, recommendations have been presented by the British Fertility Society (BFS) and the American Society of Reproductive Medicine (ASRM) relating to the number of embryos which should be transferred after in-vitro fertilization (IVF) treatment (Appendices I and II). The ASRM recommends transferring between three and five embryos for IVF with more
for gamete intra-Fallopian transfer (GIFT), whereas the BFS recommends a maximum of two. The European Society for Human Reproduction and Embryology (ESHRE) Capri Workshop (1996) recommended either two or three embryos depending on female age. Coetser and Dhont (1998) suggested that we should be moving towards the transfer of only one embryo. Since the authors of all these documents have presumably based their views on the same published data, it is interesting to speculate why they have come to such different conclusions.

All state their concern about the alarming increase in the incidence of multiple pregnancy and are anxious to ensure that the incidence of this iatrogenic complication of treatment is reduced to a minimum. The issues discussed in the USA, leading up to the ASRM recommendations were fully addressed in the debate ‘Embryo transfer and multiple gestation’ (Bavister and Boatman, 1997; Bronson, 1997; Bustillo, 1997; Faber, 1997; Palmer, 1997; Van Blerkom, 1997). With this aim in mind, the best option must surely be to transfer only one embryo. Our difficulty is to persuade clinicians to accept that the inevitable reduction in pregnancy rate which would result from a restrictive policy, is a price worth paying. Indicative of the confidence problems which surround the promotion of such a policy, is the lack of controlled prospective studies in this field. The motivation which drives embryo transfer policy is complex and is influenced by factors other than clinical studies.

Those who recommend only one embryo transfer understand that any multiple pregnancy, even twins, is best avoided. Others would argue that twins are an acceptable outcome, hence the recommendation of two embryo transfer. A recent survey by the BFS (Murdoch, 1997) of 150 CHILD members (patient support group in UK) found that 66% felt that twins would be an ideal outcome of IVF treatment. Clearly society places no stigma against twins, probably the opposite. But are patients and clinicians fully aware of the consequences in terms of obstetric and neonatal outcome of a twin pregnancy? It is estimated that a twin pregnancy has a 1 in 21 chance of losing each baby (Human Fertilisation and Embryology Authority, 1997) and the risk of producing a handicapped child from a twin pregnancy is 1 in 13 (Yokoyama et al., 1995a,b). Furthermore, there is an increase in the obstetric cost of monitoring twin pregnancies which have an increased incidence of miscarriage, pregnancy induced hypertension, premature labour, gestation diabetes, abnormal delivery (Seoud et al., 1992). In accepting a risk of twin pregnancy by transferring two embryos, we must therefore accept that this also carries a cost greater than that of a singleton pregnancy.

By advocating the transfer of more than two embryos, the ASRM must accept that high multiple pregnancies will occur. The maternal and fetal cost of such pregnancies is not disputed. Such a policy relies on the ‘escape route’ of selective fetal reduction, usually to twins. Notwithstanding the potential complications of twins as discussed above, the ethical and legal issues which surround selective fetal reduction have largely been avoided. It is more widely practised in the USA than in Europe and this probably reflects differences in prevailing ethical views. It seems unlikely that that society will allow this type of abortion to continue indefinitely. Furthermore, it seems illogical to advocate a restriction in the number of embryos to be transferred yet still transfer enough to cause high multiple pregnancies. Logic dictates that if the routine policy is to accept and advocate selective fetal reduction as the ‘safety net’, why not transfer all embryos available and achieve the highest possible pregnancy rates? Any restrictive policy relating to embryo transfer should surely aim to reduce multiple pregnancies before implantation not afterwards.

What are the views of the patients? Should clinicians, managers or politicians make the decision for them? Is it realistic to expect them to make such decisions? Can they balance the conflicting interests of society which has limited resources for neonatal care with their overwhelming desire for a baby at any cost? Can they really understand the consequences of being parents of triplets? Can they really be expected to understand the implications of selective fetal reduction when their main concern when they start treatment is that they cannot conceive? The financial implications in the UK are unique since patients are not accustomed to paying for health treatment at source. For many, paying for IVF causes additional, conflicting stresses on the decision making processes. Patients are strongly encouraged to use controversial and selective outcome data to decide from which IVF unit to buy services. The ‘bottom line’ of this complex set of published data is a comparative table of the live birth rates between centres and few will question the significance of the embryo transfer policies and the related multiple pregnancy rates. Asking patients to make an independent decision about how many embryos to transfer is unrealistic.

In the UK, there is a legal restriction which limits the number of embryos transferred to a maximum of three. In the USA, there is no such legal limit. Within these restrictions, who makes the individual decision? The BFS survey (Murdoch, 1997) showed that the decision about how many embryos should be transferred was made following discussion between the patient and the doctor although it was noted that in units which mainly transferred three embryos, the views of the patients were considered to be more important. This perhaps reflects who was considered to have taken the ‘responsibility’ or ‘blame’ for the decision. In the UK, there is widely varying practice in embryo transfer policy. Some units will always transfer two embryos when a choice is available whereas others will only transfer tree. There is no evidence of a difference between the patient population between these centres and most are paying for treatment, and so have the option to go elsewhere if they wish. It must therefore be the information given to patients by the clinician which allows them to accept the advised option. If we wish to change to overall transfer policy, we must therefore influence the views of the clinicians.

Most clinicians try to make decisions which are in the best interest of their patients. One couple might achieve a singleton pregnancy from transfer of three embryos which would not have occurred had only two been transferred. Another couple will have a handicapped triplet child rather than healthy twins. At present, we have no methods of accurately predicting outcome in individual cases. Selective advice as given by both the BFS and the ASRM may reduce the overall incidence of multiple pregnancy but the transfer of two or more embryos
will always carry an individual risk. Balancing benefit against disadvantage is not easy particularly since the benefit, increased positive pregnancy tests, is immediately appreciated by both clinicians and patients, whereas the impact of longer term consequences are more distant. It has been suggested that IVF clinicians and patients be forced to take account of the longer term consequences by paying for them (Levene et al., 1992); a warning which we should not ignore.

Clinicians are also influenced by ‘League Tables’. Although produced in the UK by the Human Fertilisation and Embryology Authority (HFEA) for the benefit of patients, they are widely used to promote centres for financial gain, hospital prestige and clinician/scientist ego. When they are so widely used by the professionals, the business managers, Health Authorities, and produced and promoted by the regulating authority, it is not surprising that the overall live birth rate data for each centre has taken on a significance disproportionate to its clinical relevance. Can we blame clinicians for using the live birth rate as the overriding index of clinical excellence? We all want to excel, so we all want high birth rates. To achieve this, more embryos are transferred.

Does the transfer of multiple embryos result in a higher pregnancy rate? The answer is definitely yes, overall. This has been proven in several statistical analyses which have been shown, when applied retrospectively to real data, to be accurate (Speirs et al., 1983; Bouckaert et al., 1994; Walters, 1996). Those who argue against multiple embryo transfer, use data to show that there is no difference in the pregnancy rate if two rather than three or more embryos transferred. These selective retrospective analyses may show no statistically significant difference in birth rate, but the mean results show consistent increases sufficient to improve a position in the ‘League Table’ and persuade patients to choose one centre rather than another. Furthermore, it is unwise to try to persuade patients that transferring multiple embryos will not increase pregnancy rates. Our instinctive gambling skills persuade us that this is not true even though we may be convinced that the odds of improved outcome are slim. We must be honest with patients in our advice and calculate the chances of success in terms of pregnancy rate and compare that with the chances of raising a happy, healthy family.

The ASRM encouraged centres to review their own data and develop their own embryo transfer policy. The most important index to consider is the multiple pregnancy rate in the centre rather than the overall pregnancy rate. The chance of success after IVF can be considered in relation to two factors. The first is the quality of the embryos. This is determined by the ovarian status of the woman which is influenced by her age, the basal concentration of follicle stimulating hormone (FSH) and the number of eggs collected. It previously also related to the sperm quality but now that intracytoplasmic sperm injection (ICSI) has overcome the fertilization problem, this is a less important feature. Finally, and perhaps most important, it depends on the quality of the embryology laboratory. Even the best eggs and spermatozoa cannot survive poor techniques or equipment in the embryology laboratory. The second factor which determines outcome, is the uterine factor. This includes all the unknown factors which determine whether or not the endometrium will respond appropriately to the embryo and allow implantation to occur. It also includes the embryo transfer technique. Embryos placed in the cervical canal or vagina will have no chance of implanting no matter how good quality they may be. These two factors can be distinguished in calculating potential success rates. If the circumstances prevail in which the embryo quality is poor, the overall pregnancy rate will be low regardless of the uterine factor and also the incidence of multiple pregnancy will be low because the implantation potential for each embryo will be poor. If embryo quality is good, and all embryos have equal potential, the chance of pregnancy will be primarily determined by the uterine factor. If, in an individual case, the uterine factor is favourable, then all the embryos are likely to implant resulting in a high multiple pregnancy rate. Accordingly, it can be seen that units with a high multiple pregnancy rate will generally be those who produce high quality embryos. Their overall pregnancy rate per embryo transfer will be decided by the uterine factor. Furthermore, this pregnancy rate will only be very slightly increased by transferring more embryos but there would then be more multiple pregnancies. Such units, i.e. those with high multiple pregnancy rates, should be advised to transfer fewer embryos. Units who have a low multiple pregnancy rate will increase their pregnancy rate more by improving their embryology service than by transferring more embryos.

Finally, Coetsier and Dhont (1998) address issues for future development. Olivennes and Frydman (1998) also look at the possible ways forward which may refine the crude methodology used at present in IVF. However, it is probably unrealistic to expect that centres will adopt a one embryo transfer policy with current technology. At present the overall implantation

### Table I. Outcome of 1199 consecutive fresh embryo transfers (ET) during 1995–1998, relating the implantation rate to the number of embryos available and the number transferred in each treatment. Pregnancies are live births or ongoing viable pregnancies (Centre for Reproductive Medicine, Newcastle upon Tyne)

<table>
<thead>
<tr>
<th>Embryos available</th>
<th>Embryos transferred</th>
<th>No. of transfers</th>
<th>Implantation rate (%)</th>
<th>Clinical pregnancy rate/ET (%)</th>
<th>Singleton</th>
<th>Twin</th>
<th>Triplet</th>
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rates are variable and, as data from our own centre show, are related to the number of embryos available (Table I). This is the best predictor at present of treatment outcome and probably reflects the overall variability in human embryos. The more that are available, the better chance we have to select good embryos for transfer so the higher the implantation rate. If embryo survivability could be more confidently predicted, then we will be able to advocate the transfer policy with more scientific accuracy. Attempts to predict the good embryo include blastocyst transfer (i.e. culling out those with poor development potential), assessing the follicle environment prior to egg collection, and evaluating the metabolism and morphology of the individual embryos. Such research is slow in providing answers. Until we can predict the embryo with high implantation prospects, we will continue to employ transfer policies which include an element of risk.

The guidelines produced by the BFS and the ARSM (Appendices I and II) draw attention to the risk of multiple pregnancy and encourage clinicians to adapt practice accordingly. The differences in their recommendations do not appear to be based on scientific fact but probably reflect the different cultural and political environments in each country.

References


The following recommendations are produced by the committee of the British Fertility Society. A fuller referenced article is published in the *Journal of the British Fertility Society* (1997) (Murdoch, 1997).
1. All possible efforts should be made to avoid multiple, particularly triplet and higher order, pregnancies.
2. Couples **must** be informed of the risks of multiple pregnancy **before** the start of treatment. centres achieving results whose confidence limits include the national average, should give the following advice. If the centre transfers two embryos in <15% of cases, couples should be advised that an average twinning rate per pregnancy of 28% and triplet rate per pregnancy of 5% can be expected. If the two embryo transfer rate in the centre is >50% of cases, couples should be advised that an average twinning rate per pregnancy of 24% and triplet rate of 1% can be expected (HFEA, 1997b). A triplet pregnancy carries a 1 in 12 chance of losing each baby, a twin pregnancy carries a 1 in 21 chance of losing each baby (compared with 1 in 113 for singleton pregnancies) (HFEA, 1997a). The risks of producing at least one handicapped child is ~1 in 13 pairs of twins, 1 in 4.5 sets of triplets.
3. The final decision about the number of embryos to be transferred should be made **before** the time of embryo transfer.
4. It should be the usual practice to transfer a maximum of two embryos in each treatment cycle.
5. Women over 38 years have a lower chance of conception following IVF and transfer of multiple embryos may improve their outcome. However there is still a risk of triplet pregnancy even at this age although it is 4.6 times less likely if the woman is >40 years compared the triplet risk if she is 30–35 years (HFEA data). Other factors such as the type of treatment (except egg donation in older women), the number of previous treatments and the number of previous pregnancies have a minimal effect on the outcome and should not be used as justification to transfer three embryos. If the embryos are of poor quality, transfer of three does not improve the pregnancy rate which will remain very low.
6. Selective reduction should be considered when there is a triplet or higher order pregnancy. However couples should also be advised of a risk of miscarriage of 15–17% after this procedure.


Multiple gestation is an unintended result of the assisted reproduction technologies (ART). Multiple gestation leads to an increased risk of complications in both the fetuses and mother.
Although multifetal pregnancy reduction is possible to reduce fetal number, its use may result in the loss of all fetuses and may have adverse psychological consequences for the couple. In addition, its use is not acceptable to some couples. Thus, reducing the number of multiple gestations produced by the assisted reproduction technologies is a worthy goal for ART programmes and their patients. These guidelines are designed to assist programs and their patients in choosing the proper number of embryos to transfer. Strict limitations, such as a maximum number of three embryos replaced by law in the UK, do not allow individual variation according to each couple’s circumstances. These guidelines may be varied according to individual clinical conditions, such as patient age, embryo quality, and cryopreservation opportunities.

1. Individual programmes are encouraged to generate and use their own data regarding patient characteristics and the number of embryos to be transferred.
2. The number of embryos transferred should be agreed upon by the physician and the treated couple, informed consent documents completed, and the information recorded in the clinical record. In the absence of data generated by the individual program, the following guidelines are recommended:
   (c) In patients with above average prognosis, (e.g. female partner under age 35) usually no more that three good embryos should be transferred.
   (d) In patients with average prognosis, (e.g. female partner age 35–40) usually no more that four good embryos should be transferred.
   (e) In patients with below average prognosis (e.g. female partner age greater than 40 or multiple failed cycles), usually no more that five good embryos should be transferred.
   (f) In donor egg cycles, the age of the donor should be used in determining the number of embryos to transfer.

Since all oocytes may not fertilize when GIFT is performed, one more oocyte than embryos may be transferred for each prognostic category.

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