REVIEW ARTICLE

IVF results: Optimize not maximize

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The desire to improve in vitro fertilization (IVF) results has led clinicians to replace more than 1 embryo in the uterus. As a result, multiple births have increased over the last 2 decades to epidemic proportions, exposing the field of assisted conception to justified criticism. This review aims to ensure that physicians involved in the field of fertility treatment are aware of the risks and complications related to multiple pregnancies, and to explore possible strategies such as blastocyst culture, preimplantation genetic screening, and embryo cryopreservation, which can help to control and reverse the tide of multiple pregnancies without reducing the good success rate that modern IVF treatment enjoys. A brief overview of the respective UK legislative system is also presented.

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Search strategy

We did a PubMed search with the key phrases in vitro fertilization (IVF), assisted reproductive technology (ART), and multiple pregnancies for articles published in English between 1990 and 2004. Also included was a selection of important review articles on the subject.

The first successful IVF pregnancy followed the retrieval of a single oocyte in a spontaneous menstrual cycle.1 Today, ovarian stimulation is considered essential for assisted reproduction in order to obtain sufficient oocytes for fertilization and subsequent selection of the best quality embryos for transfer into the uterus. Originally, human embryos were predicted to have similar high implantation rates as in animal husbandry, which were known to be in the region of 80%. However, over 25 years of experience in assisted reproduction has revealed that implantation rates above 30% are only rarely achieved. This frustratingly low rate, coupled with the availability of surplus embryos, led clinicians to increase the number of embryos transferred to the uterus per treatment cycle in order to maximize pregnancy rates. Data from 538,727 cycles performed in Europe during 1999 and 2000 revealed that more than 1 embryo was transferred in 88% of IVF cycles.2,3 The corresponding percentage in the US in 2001 was 94%.4

Indeed, higher pregnancy rates were achieved when 2 or more embryos were transferred, but the frequency of twins, triplets, and higher-order multiple gestations also increased to the extent that the high incidence of multiple gestation is now recognized as the major problem associated with ART.

The incidence of multiple pregnancies has risen at an unprecedented pace over the past 2 decades, with IVF responsible for approximately one half of all multiple

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births in various parts of the world (Figure 1). For example, the twin birth rate in 2001 in the US was 59% higher than that in 1980, while the triplet and higher-order birth rates were a staggering 401% higher. Between 1997 and 1999, ART accounted for 0.7% of all births in the US, including 0.3% of all singletons, 11.5% of all twins, and 47% of all higher-order multiple births. Furthermore, of the 40,687 infants born after ART procedures in the US in 2001, 54% were born in multiple-birth deliveries (46% were twins and 8% were triplet and higher-order multiples). The situation in Europe is no different. Between the mid-1970s and 1998, the rate of twin pregnancies increased by 50% to 60% in France and the UK, while the triplet or higher-order multiple pregnancies increased by 310% in France and 430% in the UK. During the same period, the triplets rates increased between 6- to 30-fold in Denmark, The Netherlands, Czech Republic, Switzerland, and Germany. In 1999, data from 258,460 cycles performed in 22 European countries revealed that more than one quarter (26.3%) of IVF-related deliveries involved a multiple gestation; twins, triplets, and quadruplets. Despite advice against multiple embryo transfer, the multiple pregnancy rate remained the same (26.4%) in year 2000.

**Risk factors for multiple gestations**

The combination of younger female age and multiple embryo transfer is the main cause behind the high multiple gestation rates encountered in IVF.

**Female age**

Among nondonor ART procedures, a strong inverse relation exists between multiple-birth risk and patient age. Numerous studies have shown that the live birth and multiple pregnancy rates per IVF cycle are highest until the age of 35 and decline linearly thereafter.

**Number of embryos transferred**

Templeton and Morris evaluated factors associated with the increased risk of multiple birth in 44,236 cycles performed in the UK, and showed that when more than 4 fertilized eggs are available for transfer, replacing 3 rather than 2 embryos did not change the birth rate, but significantly increased the risk of multiple pregnancy, regardless of female age. Likewise, a more recent report from the Centers for Disease Control and Prevention showed that in women <35 years of age using freshly fertilized nondonor embryos, single embryo transfer resulted in a pregnancy rate of 17% with no twins, although most of these were nonelective single embryo transfers. When 2 embryos were transferred, the overall pregnancy rate increased to 44%, but over one third of the resulting pregnancies (36.7%) were multiple gestations, including 1.1% triplets. Transferring a third embryo increased the proportion of multiple gestations to 43.7%, and of triplet pregnancies to almost 6.5%, without conferring any benefit to the overall pregnancy rate, which remained at 42% (Figure 2). A similar pattern was observed when examining data related to
ART procedures in which surplus (nontransferred) embryos were cryopreserved. 15

Hazards of multiple gestations

Multiple gestations are associated with increased health risks to both mother and babies when compared with singleton pregnancies.

Maternal risks

In addition to the prevalence of symptoms related to the larger uterine size, such as earlier general discomfort, difficulty in sleeping, and the need to stop work sooner, multiple pregnancy exposes the mother to an increased risk of developing a variety of health hazards such as hyperemesis gravidarum, miscarriage, hypertensive disorders, anaemia, urinary tract infections, glucose intolerance, antepartum haemorrhage, preterm labor, and operative delivery.17-19 One study found a relative risk of 6 (95%CI 4.1-8.9) for eclampsia in a multiple pregnancy compared with that in a singleton gestation.20 Another study estimated the relative risk of postpartum hemorrhage associated with multiple pregnancy to be between 3 and 4.5.17 Mothers with multiple gestations are also more vulnerable to the side effects of tocolytic therapy used to treat preterm labor because of increased maternal blood volume and cardiac output. Moreover, multiple pregnancies carry an increased risk of maternal mortality compared with singleton pregnancies. In 1994, a rate of 14.9% per 100,000 pregnancies has been reported in Europe compared with 5.2% for singleton pregnancies (OR 2.9, 95%CI 1.4-6.1).18

Perinatal morbidity and mortality

Fetal loss before 24 weeks’ gestation and perinatal mortality are more common in multiple gestations, the latter being mainly caused by the increased risk of intrauterine growth restriction, preterm delivery, and low birth weight (Figure 3).21,22 Martin et al17 demonstrated that the gestational age at delivery was reduced by 3 weeks for each additional intrauterine fetus, while the birth weight of the average triplet (1678 ± 574 g) was nearly half of that for the average singleton (3339 ± 573 g). Underlining the vulnerability of babies delivered from multiple gestations, one study showed that although twins comprised only 2.4% of all neonates, they accounted for 13.8% of cases of respiratory distress syndrome, and 11.4% of those with major grade of intraventricular haemorrhage.23 Another study examined the rate of admission to a neonatal intensive care unit for treatment and found it to be significantly more common in twins (48%) and higher-order multiples (78%) compared with singletons (15%).24 ART, particularly IVF techniques involving zona pellucida manipulation (such as intracytoplasmic sperm injection [ICSI] and assisted hatching) or extended in vitro culture, appear to increase the risk of monzygotic twinning, which could further contribute to the increased morbidity associated with multiple pregnancy.

Furthermore, all mortality rates (stillbirth and neonatal and infant mortality rates) were shown to be higher in multiple pregnancies. For example, twin pregnancies were reported to have a 5-fold increase in the risk of intrauterine death.30 Additionally, the neonatal mortality rate for twins was found to be 7 times higher, and that for higher-order gestations was more than 20 times higher than the rate for singleton pregnancies.30,31 Likewise, the infant mortality rate was reported to be 5 times higher for multiple pregnancies compared with that for singleton pregnancies (31 vs 6 per 1000 livebirths, respectively).32 This rate increased from 28.9 per 1000 livebirths for twins to 63 for triplets and 95.5 for quadruplets.32
**Childhood morbidity**

There is strong evidence that infants from multiple pregnancies suffer an increased risk of health and developmental problems. Twins and triplets have a 1.7- and 2.9-fold increase in the risk of severe handicap compared with singletons.33 Yokoyama et al34 found an increase in the risk of producing 1 child with cerebral palsy from 1.5% in twins to 8% in triplets and 43% in quadruplets, while Petterson et al35 estimated that the risk of cerebral palsy in twins and triplets was 5 and 17 times that in singletons, respectively. Furthermore, among infants who survive the first year of life, Pharoah and Cooke36 found the prevalence of cerebral palsy to be 0.23% in singletons compared with 1.26% in twins and 4.48% in triplets. Other markers of mental development, such as language development and motor coordination, have also been found to be delayed in infants and children from multiple pregnancies.37,38

**Psychologic impact on family**

What might have been seen as a happy ending to a long journey of childlessness may actually turn out to be the beginning of unexpected difficulties.39 Caring for twins, triplets, or more can pose significantly higher levels of physical, psychological, and financial strain on parents eager to provide the high standard of care they aspired to during many years of infertility.40-45 Additional problems, such as admission to a neonatal intensive care unit, the need for long-term rehabilitation, or death of 1 or more of the babies may prove exceptionally difficult for the family to cope with.46

A unique situation for triplet and higher-order multiple pregnancies is the consideration of multifetal pregnancy reduction. This often involves enormous emotional pain and psychologic stress that could persist for years, similar to that experienced by the bereaved parents who still have surviving multiples.47-51 As a result, anxiety, depression, feelings of regret, marital relationship difficulties, child abuse, and the use of psychotropic medication have been reported with higher frequency in parents of multiple pregnancies.42,52,53 In addition, there is evidence that first-time parents of twins after assisted reproduction experience higher level of parenting stress and lower levels of psychologic well-being compared with those who conceive twins naturally.44,54-56 Even children resulting from a multiple gestation as well as their (often older) siblings have been shown to be more prone to suffer psychologic distress46,52 and behavioral disturbances.57 More studies are needed to determine the extent of the psychosocial impact of a multiple birth, particularly after a period of infertility.44,53 This adverse impact should also be contrasted with the emotional and marital relationship strain caused by infertility and compounded by failure of IVF treatment.58,59

**Economic consequences**

Multiple gestations result in higher perinatal costs than singleton birth as a direct result of preterm birth and the consequent need for intensive care facilities.24,60-64 In one study, the hospital costs per twin pregnancy was found to be 5 times higher than those per singleton pregnancy.65 Health care, education, and social costs to society incurred during infancy and childhood are also higher for those from multiple gestations compared with singleton pregnancies.64,66-68 The latter 3 studies66-68 concluded that even when more IVF cycles are needed to achieve similar delivery rates after transfer of 1 compared with 2 embryos, the lower twin pregnancy rate in the single embryo transfer group makes this approach more cost effective. An example of implementing this approach is the “Belgian project,” in which money saved by avoiding multiple pregnancy is used to reimburse the costs of ART-related laboratory activities linked to a transfer policy aiming at substantial multiple pregnancy reduction.69

**Risk-reduction strategies**

Multifetal pregnancy cannot be regarded as an acceptable method of controlling the spiralling rate of multiple pregnancies associated with ART because of the moral, ethical, and psychologic consequences of, as well as the risks associated with, the procedure.70,71 The only realistic way to control the tide of multiple pregnancies associated with IVF is to limit the number of embryos replaced per transfer. However, this policy needs to be implemented in such a way so as not to prejudice the good pregnancy rates currently achievable per IVF cycle. Thus, the implantation rate per embryo transferred needs to be reasonably high in order to maintain acceptable pregnancy rates when only 1 or a maximum of 2 embryos are replaced. To this effect, several strategies are being developed and refined to improve the implantation potential of embryos selected for transfer.

**Identification of “high-quality” embryos**

If one could choose the most viable embryo for replacement from a cohort of growing embryos, the need to transfer multiple embryos would decrease. The presumptive quality of cleavage stage IVF embryos is thought to be closely related to their implantation potential.72,73 A top quality embryo (as assessed morphologically and developmentally) is one that has cleaved to 4 to 5 cells or 7 to 8 cells on day 2 or 3 of in vitro culture (respectively), has symmetric blastomere
sizes with no multinucleation, and has less than 20% cytoplasmic fragmentation. Transferring only 1 of these embryos has been shown to result in acceptable implantation and pregnancy rates, while substantially reducing the risk of multiple pregnancy.

Other criteria that may assist in selecting embryos with the highest implantation potential include pronuclear morphology, time to enter into the first mitotic cleavage, and measurement of the biochemical activity of cleavage-stage embryos in culture media. Combining more than one of these criteria into a composite embryo quality “score” has been proposed to further improve the process of embryo selection.

However, it should be noted that although morphologic assessment can provide useful clues when choosing the best embryo for transfer, such method has significant limitations since embryos with good morphology, particularly from older women, can carry lethal genetic or metabolic abnormalities.

Blastocyst culture and transfer

The availability of sequential culture media that are tailored to embryo requirements at various stages of development has made extended culture of embryos until the blastocyst stage feasible. Delaying embryo transfer until day 5 or 6 of in vitro culture, when the embryo has reached the blastocyst stage of development, has some theoretical advantages that may improve the success of embryo transfer procedures. Extended culture allows better identification of the developmental potential of embryos because only a small percentage of embryonic genes are activated by day 2 or 3 of culture. Owing to the fact that human embryos normally reside in the fallopian tube in their early stages of development and do not implant until after compaction, the uterine environment is also better able to cater for the nutritional requirements of a blastocyst than a cleavage-stage embryo. Thus, the ability to transfer developmentally competent embryos at a stage when they are metabolically compatible with the uterine environment should allow the transfer of fewer embryos (preferably only 1) without compromising pregnancy rates. Although data from randomized studies assessing the advantages of blastocyst transfer are still conflicting, mainly because of differences in study inclusion criteria, and there are still some concerns regarding potential (epigenetic) risks of extended embryo culture, the technique could still be a valuable tool in the challenge to reduce multiple pregnancies.

Preimplantation genetic screening

It has been suggested that the low implantation rate of IVF-created embryos is mainly caused by the fact that between 23% and 80% of human embryos generated through IVF have numerical chromosomal abnormalities. Considering these data, assessment of the chromosomal normality of preimplantation embryos can help to identify those with high implantation potential among a cohort of morphologically normal embryos. Screening fertilized oocytes as well as cleavage-stage embryos for aneuploidies using fluorescent in-situ hybridization [FISH] probes for between 5 and 14 chromosomes (mostly 13, 15, 16, 18, 21, 22, X and Y chromosomes) has been used in a number of trials aiming to improve implantation and pregnancy rates in older women and those with recurrent pregnancy loss and IVF implantation failure. Although early results are encouraging, the technique is yet to be applied as a means of reducing multiple pregnancies. Data from randomized studies in younger women on limiting the number of genetically screened embryos replaced are still lacking.

Embryo cryopreservation

The improvement in protocols of controlled ovarian stimulation and embryo culture techniques and the trend to transfer fewer embryos per IVF cycle mean that patients are more likely to have surplus viable embryos. In order to maximize the chance of pregnancy from a single egg retrieval procedure and encourage patients to choose to transfer fewer embryos, it is imperative that robust techniques of embryo cryopreservation are incorporated into routine IVF programs. One study investigated the value of cryopreservation of surplus embryos after the transfer of a single embryo in 127 patients. Replacing the frozen embryos at a later stage augmented the delivery rate from 26.8% after the fresh transfer to more than 50%, with a twinning rate of 7.6% and no triplets. Data from studies investigating the outcome of transferring single fresh and frozen-thawed blastocysts are also starting to emerge and look encouraging. It is hoped that in the near future the combination of a single embryo transfer together with a successful cryopreservation program will become the standard care for IVF treatment.

Patient education

Research has shown that a considerable proportion of infertile couples are unaware of the risks of and, hence, welcome multiple births as an outcome to their fertility treatment. This desire, combined with financial pressures on couples of having to fund their own IVF treatment and the market competition between fertility clinics, can fuel the temptation to replace multiple embryos in order to maximize success rate. However, success rate must also be balanced with consideration of effects on maternal and fetal health.
Therefore, increasing patient awareness of the risks of multiple births through counselling, providing written information as well as media coverage, can be an important strategy to reduce the incidence of twins and higher-order multiple gestations. One study showed that reassuring patients good IVF pregnancy rates can be maintained with single embryo transfer(s) may encourage patients to change their attitude towards single embryo transfer. Evidence from randomized studies supporting such practice in younger women is beginning to emerge. In a recently published multicenter trial conducted in the Scandanavian countries, Thurin et al concluded that in women under 36 years of age, transferring 1 fresh embryo and then, if needed, 1 frozen-and-thawed embryo, dramatically reduces the rate of multiple births, while achieving a rate of live births that is not substantially lower than the rate that is achievable with a double-embryo transfer. Offering financial incentives, such as a fixed charge for all embryo transfers resulting from an oocyte recovery, can further facilitate the implementation of a single-embryo transfer policy. Thus, physicians’ responsible attitude towards their obligation to protect the welfare of the patient and her future children is clearly paramount, especially where professional self-regulation prevails.

Finally, changing the way IVF clinics’ performance is measured and reported so as to place greater emphasis on the outcome of singleton healthy term babies, rather than the traditional measure of live births per ART cycle initiated, can be material in educating patients and exposing those clinics with high rates of multiple births and promote a structural change in practice.

The UK legislative approach to reduction of ART-associated multiple pregnancy

Prevention of multiple pregnancies is now viewed as a public health concern, and many countries have already passed laws or binding codes of practice (as in UK, France, and Germany) or have official guidelines set out by national scientific societies (as in US and Belgium) to ensure that measures are taken by individual clinics to minimize multiple gestations.

In the UK, the Human Fertilisation and Embryology Act was passed in 1990 and required the establishment of the HFE Authority, which was set up in 1991 as a statutory nondepartmental public body that is accountable to the Secretary of State for Health, and responsible for the licensing and monitoring of all clinics in the UK that carry out IVF, donor insemination, and human embryo research. Thus, the activities of all IVF clinics are regulated by the HFEA Code of Practice, to which they must adhere in order to receive and renew their licenses. These are normally granted for up to 3 years, subject to a satisfactory yearly inspection by the HFEA. Practicing without a license is a criminal offense that is punishable by a substantial fine and/or a custodial sentence.
In an attempt to minimize the risk of multiple gestations, the first code of practice issued by the HFEA limited the replacement of eggs or embryos to a maximum of 3 in any 1 cycle. Although this policy has been strictly adhered to by all licensed clinics, the UK continued to see a steady increase in the incidence of multiple births (Figure 4). This led the HFEA to produce revised guidelines in 2001, recommending that the number of eggs or embryos to be transferred in any 1 cycle should be reduced from 3 to 2, except in exceptional circumstances when 3 embryos could be replaced.

Although implementation of these guidelines led to a slowing down in the rate of triplets, 109 sets of triplets (1.7%) and 1597 sets of twins (25%) still were born from the 25,080 cycles undertaken in 2001. More recently, in order to strengthen its commitment to reducing the incidence of multiple births, the HFEA produced in January 2004 a new code of practice,140 which limited the number of eggs or embryos to be transferred in a single cycle to women of less than 40 years of age to only 2, with no exceptions, and regardless of the procedure used for replacement. Women aged 40 and over at the time of embryo transfer may still receive a maximum of 3 eggs or embryos. This latter regulation is enforceable as part of the license renewal procedure, and the HFEA intends to monitor this practice and review the data produced by licensed clinics.

If the aim of ART was to achieve a singleton healthy pregnancy, then multiple pregnancies should be regarded as complications. Infertility specialists have an important role to ensure that the risk of multiple pregnancies is minimized through education of patients, the health care profession, as well as policy makers. They also have a moral responsibility to reduce the risk of harm to the unborn child (and its family) that might otherwise result from multiple pregnancies. Therefore, the aim of IVF treatment should shift from maximizing the pregnancy rate per treatment cycle to optimizing the number of singleton pregnancies achieved per patient treated. The only strategy to fulfill such obligation is to adopt a policy of single embryo transfer. New developments in blastocyst culture, preimplantation genetic screening, and embryo cryopreservation are hoped to allow implementation of that policy without reducing overall success. Clinical trials assessing the usefulness of these developments in reducing multiple births are urgently needed.

References


