A Risk–Benefit Discussion of Single-embryo Transfer

a report by
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Infertility affects about 10% of couples. The negative impact of infertility can be manifold, and includes relationship breakdown, social stigma, and stress. Advances in assisted reproduction techniques (ARTs) since the first US birth through *in vitro* fertilization (IVF) on December 28, 1981 mean that success rates have increased from around 20% 10 years ago to nearly 50% in women younger than 35 years today.[1,2]

The terms 'multiple pregnancy' or 'multifetal gestation' refer to pregnancies in which two or more fetuses are present in the uterus. While the natural multiple pregnancy rate is around 0.4%, it is much higher in IVF patients (see *Table 1*).[3–8] The rate of multiple births has increased markedly in the last 20 years due to advances in ART—specifically, the increased use of drugs for ovulation induction (OI) and super-ovulation for intrauterine insemination (IUI) and IVF.[9]

Risks of Multiple Pregnancies

The greater incidence of complications associated with multiple pregnancies compared with singleton gestations is well established; most of these complications are directly related to increased rates of prematurity. More than 50% of twins and 90% of triplets are born pre-term (before 37 weeks of gestation) and with low birth weights (less than 2,500g). Peri-natal mortality (stillbirths and neonatal deaths within the first week of life) is 10 times higher for multifetal gestations than for singleton gestations. Furthermore, the incidence of cerebral palsy is seven times higher in twins and 20 times higher in triplets than in singleton pregnancies.

The economic consequences of multifetal gestations represent a significant hidden cost of ART. Additionally, the cost to the family of long-term care for disabled children resulting from a premature birth must be taken into account.

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Table 1: Risk Factors for Multifetal Pregnancy—Monozygotic Twins

Source of Pregnancy	Incidence (%)	Reference
Spontaneous	0.42	Bulmer, 1970[3]
OI and IVF patients	1.2	Derom, *Lancet*, 1987[4]
		Edwards *JIVFET*, 1986[5]
D3 IVF with AH	1.9	Alikani, *Hum Reprod*, 2003[6]
IVF with blastocyst culture	5	Behr, *JARG*, 2000[7]
IVF with blastocyst and co-culture	0	Menezo, *Hum Reprod*, 2002[8]

OI = ovulation induction; IVF = in vitro *fertilization; AH = assisted hatching.*
Source: Scott RT, Miller K, personal data.

With the huge advances seen in the field of assisted reproduction in recent years, some might ask why multiple pregnancy remains a problem. There are many reasons, including:

- the lack of efficiency of IVF cycles;
- insufficient education of couples on the risks of multiple pregnancy;
- infertility experts not being involved in the obstetrical outcome of patients; and
- the success of IVF traditionally being assessed by pregnancies rather than by healthy live births per cycle.

Recognition of these unfavorable features of multiple pregnancies has led to a move to implement measures that will limit their creation through ART.

Multifetal reduction can be used to decrease the occurrence of high-order multiple deliveries; however, reduction of twins to a single fetus is rarely performed. The risk to the pregnancy varies, but is in the order of 4.5–15.4%.[10] Psychologically, elective reduction is often difficult for couples who have suffered a long period of infertility, and may not be an option for some couples on ethical or religious grounds.

The number of embryos transferred in ART is the most important factor in determining whether a multifetal or singleton gestation will occur. Defining the point at which transferring an additional embryo did not increase or actually decreased the probability of a singleton pregnancy without substantially increasing the overall birth rate was key. One of the important studies that began the process of the issuance of transfer guidelines was that of Templeton and Morris in 1998.[11] They demonstrated that in selected—and usually younger—

Table 2: Cumulative Pregnancy Rates—Single- versus Double-embryo Transfer

Assumptions for Analysis
Drop-out rate after each cycle 40%
Pregnancy rate—SET 25%
Pregnancy rate—DET 25%
SET twin rate 2%
DET singleton rate 70%
DET twin rate 29%
DET triplet rate 1%

SET = single-embryo transfer; DET = double-embryo transfer.

women, the benefit of the transfer of multiple embryos on pregnancy rates peaks at two. The average number of embryos transferred during ART procedures has dropped from around four across all age groups in 1995 to around 2.5 in women less than 35 years of age and 3.5 in women aged 41–42 years in 2004. The result has been the avoidance of triplets without a significant drop in the overall pregnancy rate; however, there has been no real improvement in the incidence of twins, which remains at around 25%. Reducing the rate of twinning would require a shift from double-embryo transfer (DET) toward elective single-embryo transfer (SET). Evaluating the corresponding effect on pregnancy rates is vital.[9]

Success Rates of Single-embryo Transfer

A number of studies, mainly in Europe, have attempted to look at the success rates of SET—with fresh embryos as well as with frozen–thawed embryos—versus DET. In summary, the studies indicate that high success (i.e. delivery) rates in good-prognosis patients can be achieved with SET if the transfer of an additional frozen–thawed embryo is included.

In a large (661-patient) multicenter trial in Scandinavia,[12] the aim was to demonstrate equivalence of live birth rates between the two strategies. A further hypothesis was that the multiple birth rate would be lower in the SET group. Women younger than 36 years who had at least two good-quality embryos underwent either:

- transfer of a single fresh embryo and, if there was no live birth, subsequent transfer of a single frozen–thawed embryo; or
- a single transfer of two fresh embryos.

Pregnancy resulting in at least one live birth occurred in 42.9% of the DET group compared with 38.8% of the SET group. Rates of multiple births were 33.1 and 0.8%, respectively. The study showed that the live birth rate in the SET group was not substantially lower than in the DET group, although equivalence could not be declared according to the definition (the upper limit of the 95% confidence interval (CI) for the difference in live birth rates should not be >10%). However, the multiple birth rate was much lower in the SET group. The live birth rate after only fresh embryo transfer was, however, significantly lower in the SET group. The price of the higher live birth rate in the DET group was a high multiple-birth rate.

It is important to note that 17% of the women eligible for a frozen–thawed embryo in this trial did not receive the transfer because the embryos did not survive the thaw. An assessment of a clinic's cryopreservation program is clearly crucial when contemplating elective SET.

Extrapolation to the United States

The results of studies such as that detailed above cannot be extrapolated to the situation in the US. Fertility treatment is expensive, and in the US prospective parents usually foot most of the bill. This means that seeking invasive medical treatment for infertility is often the last option for the majority of couples in the US and, in consequence, the women seeking infertility treatment are significantly older than in other parts of the world. In addition, the infertility of these women is likely to be more severe, as they will have been trying to get pregnant for a greater period of time and will have already tried other less expensive options. This population is very different from that investigated in studies such as the Scandinavian experience, and is not ideal for SET. This was quite clearly demonstrated in a more recent European study that found that in unselected patients the pregnancy rate obtained with SET is half that of DET.[13]

The recognition that multiple gestations are an undesirable outcome of ART has led many countries to enact strict laws governing how many embryos can be transferred per cycle. In the UK, for example, a maximum of two embryos can be transferred in women under the age of 40 years. In Belgium, SET is obligatory in good-prognosis patients. The result of this policy is not only fewer multiple births, but also fewer live births per IVF cycle. Figures for 2000 indicate that in the US[1,2,14]—where there is no federal legislation on the practice of assisted reproduction—31% of IVF cycles led to babies being delivered compared with 19.4% in the UK and 16.4% in the rest of Europe.

Individualized Care

According to the American Society for Reproductive Medicine (ASRM), elective SET is not appropriate clinical care for all patients. Its guidelines state: "Strict limitations on the number of embryos transferred, as required by law in some countries, do not allow treatment plans to be individualized after careful consideration of each patient's own unique circumstances." This means that the ultimate decision remains with patients and physicians. However, while allowing for individualization of patient care, this also means that the decision on how many embryos to transfer may be subject to bias such as economic pressures and insurance circumstances. The US does transfer more embryos than Europe.

Another necessary consideration is that while physicians regard multiple births as an unwanted outcome, not all patients do. In fact, for many patients the relative risk of having twins will be hugely offset by specific potential benefits. There is even a potential medical benefit from twinning: there is a distinct possibility that the delay in any second conception may result in additional loss of fertility, with the net loss of a potential second child.

Typically, patients who seek IVF treatment are considered to be highly motivated, and the general impression is that these patients end treatment only if they have become pregnant or run out of funds.

However, this is not always the case. A significant number of patients drop out because of the huge physical and psychological burden of IVF treatment. In our experience, the drop-out rate is around 40% after each cycle of IVF (see *Table 2*). This high drop-out rate is a very real phenomenon and occurs even when IVF treatment is significantly subsidized, as a number of European studies into the subject have demonstrated.[15,16] Physicians have to regard patients who drop out of treatment as a failure of the treatment rather than the patient's own choice, and must attempt to address the problem accordingly. Pregnancy rates are hugely important in this scenario.

Cost-effectiveness

The economic costs of multiple pregnancies include the service charges to establish the pregnancy and see it through to delivery and any neonatal services, but should also take into account the life-long consequences of the birth of a healthy child versus that of a child with disabilities. The evaluation of cost-effectiveness is therefore neither straightforward nor without controversy. Proponents of SET have suggested that its practice is cost-effective,[9] although a complete analysis has never been performed.

Costs also vary greatly with geography: in Europe, for example, IVF is significantly cheaper than in the US. Cost-effectiveness also involves the value that an individual assigns to achieving pregnancy as soon as possible. Europe has a lower per-cycle pregnancy rate than the US, suggesting that on average European women have to wait longer for pregnancy success.

Relevant available cost data are limited; therefore, using this argument in support of SET is at this point in time misleading.

Selection

Patient selection is the most important factor in predicting success with ART. Female age is inversely proportional to IVF success rates due to increased ovarian gonadotropin resistance and deteriorating egg quality as women get older. There are ways to identify those least likely to be successful with IVF prior to cycle initiation. The most useful test to identify poor responders is taking follicle-stimulating hormone (FSH) and estradiol levels at day three. If these levels are <10mIU/ml and <70pg/ml, respectively, the patient generally has an excellent prognosis.[17,18] More information on predicting success is found in the article by Rosenwaks (see pages 5–8).

Many reproductive professionals recognize that embryo quality is more important than a woman's age in determining whether she should receive SET or DET. Generally, embryos are considered of good quality (grade) if they contain regular-sized blastomeres and little or no fragmentation. As the fragmentation rate increases, the implantation rate drops off. This is most marked in older women. One study showed that in women under 35 years of age a fragmentation rate of 26–35% reduced implantation rate to 80% and a fragmentation rate of 36–50% reduced it to just over 60%; for women aged 40 years and older the figures were around 39 and 21%, respectively (Scott, unpublished data).

Results from a recent Finnish study suggest that embryo quality rather than a woman's age should determine whether one or two embryos are transferred.[19] It was found that infertile women between the ages of 36 and 39 years with good-quality embryos had similar conception success to younger women when a single embryo was transferred. A significant area of research has to be the assessment of embryonic, and therefore reproductive, competence. Better markers of embryo quality will be crucial if we are to move toward more SETs.

Conclusion

The arguments for and against SET continue and each side has respected proponents and opponents. SET may be suitable for some infertile couples, but not all. In certain medical indications SET is wholly sensible (prior uterine surgery or pre-term labor, for example). Additionally, if the patient has appropriate medical history (less than 35 years of age, normal ovarian function, and no previous IVF failures), one might say she is an ideal candidate for SET. However, few patients fit neatly into these two categories.

The goal of all reproductive practitioners is to help patients to deliver healthy babies. If the goal is not achieved because too many unsuccessful IVF cycles caused patients to run out of funds or cease treatment because of the psychological burden, then we have failed. Individualized patient care has to be paramount, and that may come with single-embryo, double-embryo, and, occasionally, multiple-embryo transfer. ■

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