What is the most relevant standard of success in assisted reproduction?

Should BESST really be the primary endpoint for assisted reproduction?

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A major problem in IVF procedures is a high rate of induced iatrogenic complications including multiple gestations. Until now, transfer of at least three embryos followed by the subsequent elective reduction of triplet or higher order gestations to twins, single embryo transfer (SET) with cryopreservation of the remaining embryos, as well as the application of SET in unstimulated cycles, serves to illustrate the diversity characterizing the worldwide effort of achievement of pregnancy that aims to avoid possible complications. The BESST (birth emphasizing a successful singleton at term) endpoint constitutes an interesting parameter imposing the safety of SET. However, the observed success rate (11.1%) requires elucidation of the specific pattern of endometrial behaviour around the implantation window as well as its involvement in the further support of gestation. Consequently, research has to focus primarily on the improvement of technical parameters to achieve an acceptable success rate during the IVF procedures as compared with spontaneous gestations.

Key words: assisted reproduction/IVF/ICSI/success rate

Introduction

The best outcome variable in assisted reproduction technology has to be defined. The singleton gestation live birth rate per cycle initiated, recently termed BESST (‘birth emphasizing a successful singleton at term’), indicates that a couple has an 11.1% chance of delivering a single healthy baby at term (Min et al., 2004). This success rate is rather low if it is compared with the take home baby rate that has been reported so far either within ovulation induction or IVF and embryo transfer programmes (Messinis et al., 1988; Osmanagaoglu et al., 2003; Vahratian et al., 2003). The strictly defined criteria for assisted reproduction treatment limit the iatrogenic complications, but exclude a group of women with reduced fertility, such as those of increased age. However, women aged >38 years constitute a high percentage of the population participating in assisted reproduction programmes. Recently, the problem of multiple pregnancies as a complication of assisted reproduction has been recognized and specific recommendations have been made (Adashi et al., 2003; Land and Evers, 2003). However, if BESST is adopted as the primary endpoint in an IVF programme, the question arises: what treatment protocol should be adopted to ensure high efficacy and safety. The ideal outcome is high rate of singleton pregnancies resulting in healthy babies at term, avoiding multiple pregnancies and the ovarian hyperstimulation syndrome (OHSS). Nevertheless, as reported in the literature, within the context of an IVF programme there are four possibilities in terms of the outcome, i.e. low singleton rate with complications (multiple follicles), high singleton rate after fetocide with complications (multiple follicles), low singleton rate after single embryo transfer (multiple follicles) and low singleton rate with no complications (monofollicular development).

Low singleton rate with complications (multiple follicles)
The existing policy in the majority of IVF clinics both in Europe and the USA is to transfer up to three embryos, although in some of them more than three embryos are transferred. With such protocols that involve induction of multiple follicular development, the total pregnancy rate per treated cycle can be as high as 40% (Coetsier and Dhont, 1998; Templeton and Morris, 1998). However, multiple gestations represent 25–35% of these pregnancies (Centers for Disease Control and Prevention, 2002; ESHRE, 2004). Application of the methodology proposed by Min et al. (2004) to these cases will possibly provide a similarly low singleton term pregnancy live birth rate per cycle initiated.

High singleton rate after fetocide with complications (multiple follicles)

During the last 15 years, fetocide has been adopted by several groups in an attempt to reduce a pregnancy from a higher to a lower order. It has been shown that embryo reduction prolongs the pregnancy of the remaining fetuses and improves the outcome (Stone et al., 2002). Although
that proposed by Min et al. (2004). This approach, however, has been criticized as raising several ethical issues.

**Low singleton rate after single embryo transfer (multiple follicles)**

In these cases, multiple follicular development is induced as above but only one selected embryo is transferred and the rest are frozen for transfer, one at a time, in subsequent unstimulated cycles (Templeton, 2000). With this approach the pregnancy rate is not expected to be high, although recently a rate > 30% has been reported (Titiinen et al., 2003). The day of transfer may be also important and if the blastocyst stage is chosen the implantation rate may be even higher (Gardner and Lane, 2003). An advantage of this approach is the virtual elimination of multiple pregnancies with the exception of a very low risk for monozygotic twins (Tarlatzis et al., 2002).

**Low singleton rate after single embryo transfer (monofollicular development)**

This includes unstimulated spontaneous cycles and therefore only single embryo transfer. This approach was used in the 1970’s but due to the low pregnancy rate it was abandoned and the ovulation induction protocols were introduced. Thereafter, the spontaneous cycles have been used from time to time but the pregnancy rate has been low (Pelinck et al., 2002). A great advantage of such a protocol is the almost zero rate of multiple pregnancies with no risk of OHSS. However, this approach may not be cost-effective if adopted in every IVF Unit.

**Comments and recommendations**

It is clear from the above alternatives that there is no uniformity within the treatment protocol for IVF. Differences exist not only between countries but also between centres in the same country (ESHRE, 2004). These differences primarily arise from current legislation as well as the attitude of local communities. An ideal outcome within an IVF programme would be a singleton term pregnancy live birth rate per initiated cycle that is > 20% with no complications. Such an approach, however, is very difficult at the moment. Prospective studies including younger women with good quality embryos, where single embryo transfer was performed, led to a substantial reduction in the percentage of twin gestations, maintaining pregnancy rates at 32–40% (Vilska et al., 1999; Gerris et al., 1999, 2004). Nevertheless, women of advanced age would not benefit from such an approach.

A reasonable compromise is a pregnancy rate that will result in the delivery of one or two healthy babies after the 34th week of gestation. Preterm delivery is a reality that cannot be avoided even after single embryo transfer (Ericson et al., 2002) and therefore its inclusion in the statistics is inevitable. Nevertheless, differences in legislation and attitudes in different communities make it difficult for infertility experts to reach a consensus in terms of a protocol that would result in the best outcome within an IVF programme. Prospective, multicentre, randomized, controlled studies are needed to provide more data on how to improve the success of treatment and increase efficacy and safety.

Due to the various protocols for ovarian stimulation, it is evident that the expression of the results as the ‘BESST’, although easy, is not descriptive of the complete outcome of the procedure, if the intention is to define the safest but not necessarily the most effective method. Despite the fact that twin pregnancy represents a high risk factor for poor prognosis (Bergh et al., 1999; Dhont et al., 1999), women who take part in assisted reproduction treatment are not discouraged and only 6.4% oppose the idea of twin gestation, while only 20% on average accept single embryo transfer (Pinborg et al., 2003). The prospect of delivering a healthy baby does not seem to deter women from the associated risks. The two possibilities are to accept the current situation, i.e. singletons and multiples (mainly twins) with a pregnancy and delivery rate > 20% per cycle initiated, or to agree that only single embryo transfer is acceptable with or without ovarian stimulation. In that case, efforts should be directed towards improving the implantation rate by focusing research on the endometrium. Improved outcome with IVF treatment may also be possible through improvement in culture and cryopreservation conditions. Theoretically, one could also use cloning technology, i.e. removal of blastomeres from a single embryo and generation of new individual embryos that could be transferred one at a time. The ethical issues of such an approach are very complex.

In conclusion, BESST as defined by Min et al. (2004) may not be the best outcome variable in an IVF programme. Although it is an interesting primary endpoint, it is still early for conclusions to be drawn regarding successful pregnancy in humans. The proposed methodology has several limitations that need to be addressed before IVF treatment can provide rates of singleton and multiple pregnancies similar to those of natural conceptions.

**References**


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