Single Embryo Transfer

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Foreword

In 1980 in the United States, that is before in vitro fertilization (IVF) or the widespread use of ovulatory drugs, some 1.8% of all births were multiple – mostly twins. By the mid first decade of the twenty-first century, this figure has doubled and many of the births have been of triplets or more. Other nations have had a similar experience.

This is no trivial matter.

Fortunately, most neonate twins and triplets are normal, but multiples have problems – even twins – and these problems can be serious, such as mental retardation.

Many reproductive endocrinologists and other users of ovulatory drugs are really not focused on the plight of multiples for the simple reason that in this age of specialization they do not participate in the obstetrical or pediatric care of their successful patients.

In this twenty-first century, it is truly time that those called upon to overcome infertility strive to produce not a baby, but a normal healthy baby.

If these observations have merit, every reproductive endocrinologist or other user of ovulatory drugs would benefit his or her patients by reading the first chapter of *Single Embryo Transfer*. This chapter by Wennerholm titled, "The risks associated with multiple pregnancies" spells out the reasons to do everything possible to avoid multiples.

For those who use ovulatory drugs, one of the things possible is elective single embryo transfer (eSET) by those who use IVF and have a patient to which it can be applied. *Single Embryo Transfer* is

a comprehensive and authoritative resource to consider and to apply the option of eSET.

Before further consideration of eSET as a solution to the problem of multiples, an overall view of the cause of multiples might be in order.

Multiples can occur naturally or by ovulation induction or ovulation enhancement (OI/OE) or by IVF. Using 2003 data of the United States Bureau of Vital Statistics [1], it was shown that for all twins 60% were natural, 8% were caused by IVF and 32% by OI/OE. For triplets, 20% were natural, 14% were caused by IVF and 66% were caused by OI/OE.

Ovulation induction/ovulation enhancement is far more responsible for multiples and their problems than IVF. These data point to the proposition that many patients now treated by OI/OE might well be good candidates for IVF if they qualified for eSET.

It is significant that some of the physiological principles of eSET so well covered in this book also are fundamental to IVF in general. Thus, these chapters are well worth the attention of all who use IVF in any form.

We might mention a few. We still struggle to identify the egg, sperm, or embryo which has pregnancy potential. To be updated on this elusive goal will be rewarding. Thus, a reading of Chapter 2 by Van Blerkom titled, "An overview of determinants of oocyte and embryo developmental competence: specificity, accuracy and applicability in clinical IVF" will be extremely rewarding as will be a reading of Chapter 8, "Sequential embryo selection for single embryo transfer" by Lynette Scott.

Oddly enough, not all IVF programs have the capability of cryopreservation. In this twenty-first century, such a capability is essential. The rationale and options for cryopreservation as practiced in Europe and America are set out in Chapters 9A and 9B, specifically, 9A by Tiitinen titled, "Cryo-augmentation after single embryo transfer: the European experience," and Chapter 9B by Meintjes titled, "Cryo-augmentation after single embryo transfer: the American experience."

These few examples and others show that *Single Embryo Transfer* deals with topics which should be mastered by all of those who practice IVF in any form.

Those who pioneered IVF share a heavy responsibility for its unintended complications and for their elimination.

The use of eSET when applicable would be a giant step to a better reproductive world. *Single Embryo Transfer* admirably points the way.

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Preface

The idea to transfer just one embryo in a treatment cycle of in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) was launched 10 years ago [1] and applied in a first series of patients with medical contraindications for multiple pregnancies [2]. These included women with diabetes mellitus, congenital anomalies of the uterus, isthmic insufficiency or with a history of early loss of (multiple) pregnancy.

Ten years later, SET (single embryo transfer) has acquired a certain place in the practice of IVF/ICSI. This place is by no means uncontroversial. Intended to be a reasonable answer to the very high proportion of multiple pregnancies [3, 4], it has been advocated vividly by some clinicians [5] and antagonized by others [6].

During the last few years, numerous articles have appeared that have addressed varying aspects of SET: patient selection, embryo selection, health-economic aspects, the definition of what counts as a success and what as a complication, the complication itself, counseling, patient's autonomy, impediments to SET, arguments in favor or against SET. It seems that the possibility of SET has provided a new and invigorating perspective to IVF. Single embryo transfer has allowed us to study the relationship between the morphology of individual embryos and their implantation potential, the true incidence of monozygotic twinning and, to some extent, the black box of early pregnancy. Single embryo transfer illustrates that "good clinical practice" for some consists of transferring just one embryo in over 80% of their patients, whereas others transfer three

or more embryos in first attempts. These contrasts suggest that although under certain circumstances the application of SET can be considered, the process of finding an appropriate place for SET is far from concluded. Single embryo transfer has led some clinicians to consider less aggressive stimulation schemes on the basis of the assumption that less eggs are needed because less embryos are needed and cryopreservation does not work too well anyway. All of this remains open to debate. Some have tried to give natural cycle IVF or minimally modified natural cycle IVF a place in the spectrum of possibilities. Single embryo transfer has introduced the notion of patient-friendly IVF or minimally invasive IVF. Some are delving deep into the embryo to single out the 100%-implanter by studying chromosomes and metabolism. All in all, the introduction of SET has spurred reflection over the whole range of aspects related to IVF treatment.

The goals of this book are several. It is not our goal to convince or to criticize, but to make aware. We defend the value of a neutral view based on data for all to see and use to the perceived benefit of their patients. What SET is, should be or cannot be depends in a very large measure on societal factors for which practicing physicians cannot be held responsible. So, whether SET is applied in up to 80% of an IVF population, as is the case in some Scandinavian countries, or given no place at all, is not problematic *in se*. More problematic is the fact that complications of multiple pregnancies are minimized or the fact that prevention of triplets is considered a goal worth achieving whereas decreasing the huge incidence of twin pregnancies is not. There is an impact in this debate of semantics. What *is* a complication? What is a risk? For some, a twin pregnancy *is* a complication, for others it *may but not necessarily entail* complications, for others a human twin pregnancy has the status of normal reproductive activity given the possibilities of perinatal medicine *anno* 2008.

Nevertheless, it is generally accepted that multiple pregnancies constitute the most frequent and serious (cause of) complications of IVF/ICSI. Both higher-order multiple and twin pregnancies do entail, in a different degree of frequency and of severity, a number of sequels that affect the children, the mother, the parents, the families and society as a whole.

It is also recognized that limiting the number of embryos to transfer is the only effective method to decrease the incidence of multiple pregnancies. However, due to the societal circumstances in which IVF/ICSI is performed, limitations on the number of embryos to transfer and more specifically the introduction of SET has been met with more enthusiasm in some countries than others. Whereas in some countries, laws regulate the number of embryos to transfer, in others, different mechanisms have been employed to decrease the twinning rate. In others still, the debate is just beginning or there is even an anti-SET attitude.

In order to safeguard its potential value and at the same time acknowledge its limitations, we think that the time is ripe to assess the possibilities and limitations of SET.

On a couple of things there seems to be increasing agreement.

First, SET works. Countries where it is implemented on a large scale, have seen their multiple pregnancy rates drop dramatically without the much feared decrease in their own pre-SET pregnancy rate as a consequence of the introduction of SET. This is, e.g., the case in Sweden, Finland and Belgium. In contrast, the overall pregnancy rate in countries where SET is difficult to introduce, e.g. the United States of America, is significantly higher, but at the price of a much higher rate of multiple pregnancies. We should try to find an equilibrium between results and complications, which is acceptable *in that particular society*.

Second, SET has spurred embryologists to search for more effective methods of embryo selection. Because morphological criteria are and will probably remain for some time to come the cornerstone of embryo selection, there has been a great effort to optimize the use of traditional morphological criteria and to validate new criteria [7]. Other, non-invasive, methods of embryo assessment, derived from their metabolic activity, are the

focus of research. Invasive techniques, such as aneuploidy screening, have also been proposed [8]. Much of this is the consequence of the increased need to select the high implantation potential or top quality embryo.

Third, SET seems to do more than just decrease the number of twin births, thereby increasing the obstetrical and neonatal outcome of the average child after IVF/ICSI. Singletons born after SET perform as well as naturally conceived singletons; and singletons after SET perform better than singletons after double embryo transfer [9, 10]. The allegedly decreased outcome of singletons after IVF/ICSI on the basis of meta-analysis of IVF/ICSI comprising all transfers (from one to many embryos) in all cycles (first until high rank trials) in all patients (young and old) reflects an average that does not exist, since both good prognosis patients (the ones that used to end up with twins in first cycles after two-embryo or three-embryo transfer) and bad prognosis patients (the ones that ended up with singletons after transfer of many embryos in high rank trials) were included in this analysis [11]. On the other hand, it has to be admitted that this meta-analysis is based on very large numbers of pregnancies and children, whereas the data on SET children have considered much smaller numbers.

Fourth, SET is a prism through which the light of assisted reproductive technology (ART) breaks into new perspectives. Patient counseling has become very important. Cryopreservation has been upgraded from a solution for an ethical problem (what to do with supernumerary embryos?) to a goal in itself (how to optimally use one oocyte harvest?) [12]. Oocyte harvest (what is achieved with the total number of eggs retrieved in a single oocyte pick-up, replaced in both the fresh and subsequent thaw cycles), and certainly not an individual embryo transfer, has become the clinical, financial and philosophical unit of thinking in IVF/ICSI. Even the definition itself of what success is, has been the topic of an international debate.

Many of these effects of SET are still under discussion, as is SET itself. Each country, each region, each center has to find out for itself whether and how to introduce SET. Financial constraints (patients having to pay for ART but not for neonatal costs), league-tables (mixing up soccer with medicine) and other imperative conditions make it much harder for some centers to adopt SET than for others. For that reason, the editors of this book explicitly aim at giving a free voice to different convictions and tendencies which are present in different parts of the world. There is no better and worse, just difference. From those differences, we can all learn. Conditions in which we work may change more quickly than we can imagine.

Generally speaking, the will to optimize IVF/ICSI outcome and the readiness to accept the birth of a healthy singleton as the ideal outcome are present.

We hope that bringing together expert opinions, often from pioneers and opinion leaders in the world, on varying aspects of SET, from the clinical to the embryological, from the patient perspective to the insurer's perspective, may help the open-minded reader to see for her- or himself what best use can be made of SET in her or his particular practice. All should strive towards an ideal start for tomorrow's children.

For SET to work, four elements are critically important: (1) creating awareness among all practitioners, patients and other stakeholders of reproductive medicine; (2) creating a continuous marketing effort of SET; (3) creating agreement and adjustment among clinical embryologists regarding embryo criteria for selection prior to transfer or/and cryopreservation; and (4) increasing access to treatment by creating funding or financing of ART which keeps a balance between social justice and a reasonable remuneration of all practitioners. These principles are meant to be applicable worldwide, not only in the richer parts of the world but in third-world settings as well.

This book can be of interest to all involved directly or indirectly in IVF and ICSI: physicians (reproductive endocrinologists, pediatricians, gynecologists, urologists, general practitioners, etc.) patients, embryologists, nurses and midwives, counseling and mental health specialists, administrative

personnel, insurers, politicians and technocrats, civil servants of governments concerned about reproduction as a public health issue, ethicists and philosophers, and medical journalists. Single embryo transfer is a sign of maturation of IVF/ICSI and all who speak out on it must take their responsibilities. This holds for all countries, whatever their actual position, since it is likely that SET will slowly be implemented until it has attained a level of universal judiciousness that can be shared by the large majority of those involved.

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