Refuting a misguided campaign against the goal of single-embryo transfer and singleton birth in assisted reproduction

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ABSTRACT: Much recent progress has been made by assisted reproductive technology (ART) professionals toward minimizing the incidence of multiple pregnancy following ART treatment. While a healthy singleton birth is widely considered to be the ideal outcome of such treatment, a vocal minority continues a campaign to advocate the benefits of multiple embryo transfer as treatment and twin pregnancy as outcome for most ART patients. Proponents of twinning argue four points: that patients prefer twins, that multiple embryo transfer maximizes success rates, that the costs per infant are lower with twins and that one twin pregnancy and birth is associated with no higher risk than two consecutive singleton pregnancies and births. We find fault with the reasoning and data behind each of these tenets. First, we respect the principle of patient autonomy to choose the number of embryos for transfer but counter that it has been shown that better patient education reduces their desire for twins. In addition, reasonable and evidentially supported limits may be placed on autonomy in exchange for public or private insurance coverage for ART treatment, and counterbalancing ethical principles to autonomy exist, especially beneficence (doing good) and non-maleficence (doing no harm). Second, comparisons between success rates following single-embryo transfer (SET) and double-embryo transfers favor double-embryo transfers only when embryo utilization is not comparable; cumulative pregnancy and birth rates that take into account utilization of cryopreserved embryos (and the additional cryopreserved embryo available with single fresh embryo transfer) consistently demonstrate no advantage to double-embryo transfer. Third, while comparisons of costs are system dependent and not easy to assess, several independent studies all suggest that short-term costs per child (through the neonatal period alone) are lower with transfers of one rather than two embryos. And, finally, abundant evidence conclusively demonstrates that the risks to both mother and especially to children are substantially greater with one twin birth compared with two singleton births. Thus, the arguments used by some to promote multiple embryo transfer and twinning are not supported by the facts. They should not detract from efforts to further promote SET and thus reduce ART-associated multiple pregnancy and its inherent risks.

Key words: embryo transfer / single-embryo transfer / pregnancy / multiple pregnancy / assisted reproduction

Introduction

For most infertility patients, single embryo transfer strategies are inappropriate. Twinning . . . deserves further investigation as a potentially useful tool for safe, cost effective improvement in population growth in countries with low birth rates. In such countries, governments may find that subsidizing IVF may represent a cost effective tool at improving birth rates (Gleicher and Barad, 2009).

In 1997, Faber challenged our field stating, ‘In the practice of advanced reproductive medicine we have progressed from the miracle baby to the day of the litter’ (Faber, 1997). His words were prescient of media-frenzied aberrations like Octomom (Stillman, 2010). Transfer of multiple embryos became open to critique as implantation rates continued to improve and more higher order multiple pregnancies (triplet or higher plurality) resulted (Templeton, 2000; Jones and Schnorr, 2001; Alper, 2004), subjecting a significant and growing number of women and their children to the much higher morbidity and mortality associated with such pregnancies. It was noted, ‘infertility specialists started doing too good a job clinically, but not as good a job in responding to the progress’ (Stillman, 2007). The 2003 Bertarelli Foundation conference ‘Infertility therapy-associated multiple pregnancies (births): an ongoing epidemic’ (Adashi et al., 2003), addressing both widespread ovulation enhancement (Jones and Schnorr, 2001) and IVF, stated that ‘the discipline of ART subscribes to the principle of responsibility towards both the patients and their children. . . . Infertility therapy-associated multiple gestation constitutes a major physical, psychological and financial challenge to couples and their children as well as society as a whole’. In 2003, the ESHRE Consensus Conference reviewed the risks and complications of
ART and concluded that the ‘essential aim of IVF/ICSI is the birth of one single healthy child, with a twin pregnancy being regarded as a complication’ (Land and Evers, 2003). The number of embryos that can be transferred in assisted reproductive technology (ART) cycles is now regulated in well over a dozen countries around the world, including Canada, the UK (http://www.hfea.gov.uk/code.html), Portugal, Greece, Germany, Belgium, Switzerland, Austria, Hungary, Italy, Sweden, France, Turkey, India, Estonia, New Zealand and Japan (Bissonnette et al., 2011; Maheshwari et al., 2011). And while the USA has so far avoided similar governmental regulation, the Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) first published practice guidelines recommending maximum numbers of embryos per transfer in 1998, with periodic subsequent updates, most recently in the past year (ASRM/SART, 2012; ASRM/SART, 2013).

Improvement in all facets of ART, coupled with a subsequent steady decline in the average number of embryos transferred per cycle, led to a marked reduction in the multiple pregnancy rate worldwide (De Neubourg et al., 2006; Van Landuyt et al., 2006; Stillman, 2007). This decrease has been most evident and universal in the reduction in higher order multiple pregnancy, while the effect on twin gestation has been much less geographically consistent (ASRM, 2012; Maheshwari et al., 2011). Some countries, with incentives by insurance coverage or regulatory support for ART treatment, coupled with restrictions on the number of embryos that may be transferred, have seen significant declines in twin gestation (De Neubourg et al., 2006; Van Landuyt et al., 2006; Wang et al., 2009). Other nations, generally without such incentives, have shown less progress to date (e.g. UK) (Chambers et al., 2013) or even modest increases in the incidence of twins (e.g. USA) (ASRM, 2012).

Recent publications detail the extent to which single-embryo transfer (SET) reduces perinatal morbidity and mortality relative to double-embryo transfer among ART pregnancies. A meta-analysis of perinatal outcomes in assisted reproduction (Grady et al., 2012) demonstrated that elective SET (eSET) was associated with a substantial decrease in preterm birth (relative risk 0.37) and low birthweight (relative risk 0.25) compared with patients having a double-embryo transfer. A second study analyzed perinatal mortality rates among the more than 50,000 children born in the New Zealand and Australia registry from 2004 to 2008. Among ART children resulting from fresh embryo transfer, perinatal mortality rates for double-embryo transfers were 58% higher relative to single-embryo transfers (Sullivan et al., 2012). These authors concluded that ‘for ART births, the most critical factor for perinatal mortality is the number of embryos transferred . . . there is justification for advocating SET as the first line management in ART with the aim of minimizing preventable perinatal deaths’ (Sullivan et al., 2012). These data support our ability to ameliorate the considerable risks to mother and fetuses found in even twin gestation following ART therapy.

Despite this growing supportive evidence and strong statements and guidelines by professional societies intended to reduce twin pregnancies through encouragement of greater use of SET, and government mandates in some cases, there still remains resistance to SET among a proportion of clinicians providing infertility treatment. In most countries around the world from 2003 through 2005, fewer than 20% of all transfers were of single embryos, with an especially low uptake of SET in the USA (Maheshwari et al., 2011). While increasing steadily, especially in some centers (Stillman et al., 2009), even as late as 2011, eSET was performed in only 12% of all IVF cycles among patients under 35 years in the USA (http://sart.org/). Among the various reasons why IVF professionals may choose not to perform SET is that many do not want to prevent twins and do not see twin pregnancy as a complication (van Peperstraten et al., 2008a,b). Following the firm stance adopted at the ESHRE Consensus Conference that the goal of treatment is a healthy singleton birth with twins being a complication (Land and Evers, 2003), several practitioners have published objections to this position (Dickey et al., 2004; van Wely et al., 2006; Belaisch-Allart, 2007). One group in particular has argued the benefits of twins and inappropriateness of SET for most patients more frequently, comprehensively and passionately than others (Gleicher and Barad, 2006, 2008, 2009, 2013; Gleicher, 2011, 2013). Their campaign has gained some surprising traction and adherents, with adverse consequences of these efforts being evident not only within some clinics and among many patients, but also among legislative and regulatory bodies who have taken note, despite the obvious flaws in the arguments. The arguments have received exposure through lectures and debates on the subject, in addition to publications in medical journals, including an invited commentary in this journal earlier this year, thus legitimizing and lending credibility to their argument. But, since so many patients, having faced considerable burdens of infertility and infertility therapy, have been spared the risk of lifelong disability, if not mortality, for themselves and their long awaited offspring through the increase utilization of SET and the goal of singleton birth, a counterpoint to the efforts to delegitimize these goals seems warranted.

**Four tenets of the campaign against SET**

The four basic tenets of the campaign to delegitimize SET and singleton pregnancy as a primary goal in ART can be summarized as:

(i) Autonomy: Let the patients decide.
(ii) Efficacy: Two embryos are more successful than one.
(iii) Cost-effectiveness: Two at once is cheaper.
(iv) Safety: One twin pregnancy is as safe as two singletons.

**Autonomy: let the patient decide**

The strongest argument in favor of twinning may be the infertile woman herself . . . Infertility patients are highly educated and well aware of the fact, as documented by reports they are willing to take very specific risks rather than face the chance of no pregnancy (Gleicher and Barad, 2009).

A patient’s decision-making certainly plays an important role in selection of the number of embryos for transfer. Few advocate limiting this bioethical principle within their clinics by mandatory SET, except when medically required. But it also must be recognized that: (i) autonomy is predicated upon truly informed consent; (ii) there are important factors which may limit autonomy; and (iii) there are counterbalancing bioethical principles to autonomy.

**Informed consent**

Informed consent, leading to autonomous patient decision-making, is a fundamental component of ethical medical treatment. Truly informed consent requires a clear understanding and appreciation of all of the risks and benefits associated with alternative treatment options. Some studies report clear majorities of patients prefer twins to singletons (Gleicher et al., 1995; Pinborg et al., 2003; Hojgaard et al., 2007),
although others suggest that these patients are a minority, albeit still quite a noteworthy preference (14–41%) (Kalra et al., 2003; Child et al., 2004; Murray et al., 2004; Ryan et al., 2004, 2007). We hear ‘But I want twins’ nearly daily in clinics, especially from nulliparous patients, from those with a longer duration of infertility and from those with more unsuccessful treatments. It is understandable that these patients are more likely to prefer multiple pregnancy (Groban et al., 2001; Child et al., 2004; Ryan et al., 2004; Hoijgaard et al., 2007) and less likely to favor SET (Blenborn et al., 2007; de Lacey et al., 2007).

Numerous studies, however, demonstrate that patients with a more complete and accurate awareness of the risks consider twin pregnancies to be less desirable (Groban et al., 2001; Child et al., 2004; Ryan et al., 2004, 2007; Newton et al., 2007) and are more accepting of eSET (Newton et al., 2007; Stillman et al., 2009; Hope and Rombouts, 2010). So, with truly informed consent, a patient’s autonomous decision-making alone will often limit the number of embryos chosen for transfer (van Peperstraten et al., 2008a,b). The more we take a responsibility to ensure that all patients are highly educated when leaving our consultation rooms, the more the patients realize that multiple gestation has significant risks. When we abrogate our responsibility to educate, an uninformed patient’s autonomy can lead them to seek multiple gestation (Stillman et al., 2009; ASRM/SART, 2012). Let us remember the role physician acquiescence played in actualizing the octuplet birth following Nadya Suleman’s exercise of her autonomy (Stillman, 2010).

**Legitimate limits and/or influences to patient autonomy**

Twins . . . represent a very obvious economic net benefit to society, with such benefits being even further enhanced in societies of the developed world, which in recent years have been struggling with decreasing birth rates and aging populations . . . such societies may benefit from subsidizing infertility treatments and maybe, even to the delivery of twin pregnancies (Gleicher and Barad, 2008).

**Government support for assisted reproduction.** Public policy mandating coverage for ART is often predicated on restrictions on the number of embryos transferred (contrary to the dubious notion of population growth or nation building through twinning). Whether the origins of that public policy are humanitarian (family building), justice (fair distribution of services) or beneficence (doing good for individuals and welfare of children and society), patients who elect to opt in to public financial support relinquish some autonomy (Bissonnette et al., 2011). Government support for ART with embryo transfer restrictions has proven to be a fiscally sound, self-sustaining policy as well, as the cost savings from the reduction in prenatal and neonatal complications of multiple pregnancies pays for the continuation of the subsidy (Chambers et al., 2011). ‘While clinical guidelines and education campaigns have an important role to play, funding remains a key element in the promotion of SET’ (Chambers et al., 2013). However, since not all transfers should be single, it is important that any governmental statutory limitations on autonomy by requirements for SET be derived using appropriate clinical criteria. This will promote a fair balance between patients’ rights and treatment efficacy and risks (Alper, 2004). Otherwise pregnancy rates may decline (Tiihinen et al., 2003; Bissonnette et al., 2011).

**Insurance or refund guarantee programs.** For patients without governmental or insurance support for ART, the more they must pay for each subsequent treatment cycle, the more embryos they are likely to transfer, intending to maximize the chance that at least one embryo will implant. Thus, for many couples, the decision to transfer multiple embryos is influenced not only by the exasperation of repeated treatment failures they often voice with ‘I will worry about it when it happens’, but also by an increased immediate economic burden of another cycle of therapy if required (Stillman et al., 2009; Martin et al., 2011). Conversely, there is a greater election of SET if the couple does not have the financial burden of paying for the next treatment, whether through insurance coverage (Coetzee et al., 2007; Stillman et al., 2009) or ethically rigorous refund guarantee programs (Stillman et al., 2009). This is as intuitive as it is statistically significant. And like government support, increased availability of insurance coverage can be predicated on clinically grounded restrictions on the numbers of embryos transferred, and its consequent reduction in short- and long-term maternal and neonatal costs. Patients can then elect whether to opt in or out of such coverage and its restrictions, and insurance companies themselves, like the patients they serve, stand to gain. An innovation recently introduced by one US insurance provider is if a patient elects SET, the cryopreservation and subsequent thaw/transfer cycle, if needed, will be a covered benefit (Rosenthal, 2013). More and expanded coverage options that serve the best interests of patients and insurance companies alike are needed.

**Counterbalancing bioethical principles to autonomy**

Beneficence (doing good), in the context of assisted reproduction, is widely accepted to mean good not only for a particular patient, but also for their children and society as well (Adashi et al., 2003). The potential children, those at greatest risk of the complications associated with multiple pregnancy, are unable to advocate for themselves. It is the professional and ethical responsibility of the physician-led clinical team, i.e. those in the best position to understand the medical risks, to advocate on their behalf. The act of ‘doing good’ for the children, for society and even for their potential parents need counter unchecked autonomy.

Non-maleficence, ‘at least do not harm’, is often stated as the bioethical principle which must be fulfilled as a prerequisite to considering the others (beneficence, autonomy, justice). The latest publications in this arena (Grady et al., 2012; Sullivan et al., 2012) further contradict the campaign supporting twinning. These studies again demonstrate that the harm imposed by perinatal morbidity and mortality in gestation following ART is markedly reduced with the use of SETs. Ask any perinatologist. Ask many of the parents of prematurely delivered twins.

**Efficacy: two embryos are more successful than one**

the currently widely advocated switch from 2-embryo transfer to eSET reduces a much smaller twinning risk, but at the expense of lower pregnancy rates (Gleicher and Barad, 2006).

The second major argument put forth by the various groups promoting the benefits of twin gestation is that randomized clinical trials (RCTs) demonstrate that double-embryo transfers yield higher success rates than single. There are several counterpoints. First, not all RCTs do demonstrate a difference in SET versus double-embryo transfer outcomes, for example, Gerris et al. (1999) demonstrated no difference in ongoing pregnancies following cleavage-stage embryo transfers, while much more recently the transfer of a single euploid blastocyst was reported to result in the same ongoing pregnancy rate (>60%) as the transfer of two untested blastocysts (Forman et al., 2013). Second,
most RCTs do not assess the cumulative pregnancy rates (including transfers of cryopreserved embryos) per ovum pickup (Criniti et al., 2005; Fauque et al., 2010).

Is it really ethically acceptable to urge … [even younger women] to reduce their immediate pregnancy chances. After all, not all frozen embryos survive thawing. No patient can, therefore, ever be guaranteed that she will be given a second chance to conceive once she decides to split the initial 2 ET chance into two consecutive eSET cycles (Gleicher, 2013).

It is true that most RCTs comparing single transfers of either one or two embryos have demonstrated that pregnancy rates are higher when two embryos are transferred (Pandian et al., 2009). However if, as supporters of twinning advocate (and as we will address below), it is appropriate to compare the cumulative risks for comparable outcomes (two children by either one twin or two singleton births), the same should apply to comparisons of transfers of equivalent numbers of embryos (e.g. one double-embryo transfer versus two consecutive SETs). eSET allows for the cryopreservation of a good quality embryo that would otherwise have been transferred and can be used at a later date for an additional pregnancy or chance at pregnancy. Steady improvement in those cryopreservation techniques has led to improvement in implantation, pregnancy and delivery rates from vitrified embryos, and this adds to even greater success in this cumulative schema (Loutradi et al., 2008; Hong et al., 2009).

Thus, this apparent choice between singleton transfer and higher pregnancy rates represents a false dichotomy, as RCT and non-randomized studies have consistently shown that the cumulative chances of pregnancy and birth per cycle are no lower with eSET than with multiple embryo transfer when the subsequent transfer of additional cryopreserved embryos is included (Thurin et al., 2004; Criniti et al., 2005; Henman et al., 2005; Le Lannou et al., 2006; Bechoua et al., 2009; Pandian et al., 2009; Clia et al., 2012). The appropriate calculation for cycle pregnancy efficacy should not be one embryo transferred versus two, but rather $1 + 1 \geq 2$, with potentially safer outcomes for all.

in unselected patients eSET significantly reduces pregnancy rates in comparison to 2-embryo transfers (Gleicher and Barad, 2006).

The third counterargument is that RCTs are not necessarily the best means by which to determine SET policies. Rather, the use of SET should be determined by patient and embryo selection within the expanding set of patients and cycles with a good prognosis. And for those patients with poorer prognosis, it is appropriate to consider the transfer of more than one embryo. Twins could be an acceptable risk of such a strategy if both should implant. The case in support of SET does not presuppose that all transfers be singleton. The same should be said for RCTs without selection.

Cost-effectiveness: two at once is cheaper

cost assessments … should be calculated in reference to … the number of newborn infants. … This alone would most likely eliminate the claimed cost advantages of singleton pregnancies … when the potential long-term earning power of a (second) human being is considered after twin delivery in the presence of a very low risk of lifelong handicaps, we conclude that twins offer considerable economic benefit to society over singleton deliveries (Gleicher and Barad, 2009).

Relative cost-effectiveness depends on the healthcare system and services offered as well as the financial system through which healthcare costs are paid, making most broad generalizations difficult. However, several independent studies from various countries have all reported estimates, suggesting that prenatal and neonatal healthcare costs are substantially higher (by 35–264%, in the order of several thousands of euros or equivalent) for one ART twin delivery compared with two ART singleton deliveries (Koivurova et al., 2004; Lukassen et al., 2004; Ledger et al., 2006; Chambers et al., 2007). This higher cost of twins offsets any savings in IVF treatment costs gained by achieving the same desired number of children more quickly through double-embryo transfer rather than SET. In a randomized trial, the cumulative treatment and pregnancy-associated healthcare costs from IVF treatment through 6 months after birth per live born child were similar between SET and double-embryo transfer groups (Kjellberg et al., 2006). And these calculations do not include any increase in costs for long-term disabilities and chronic medical conditions associated with the higher prematurity and lower birthweights of twins relative to two children carried as singletons.

Safety: one twin is as safe as two singleton pregnancies

The correct statistical comparison of risks … is … not between a twin delivery and one singleton delivery (as in the obstetrical paradigm) but between a twin delivery and two singleton deliveries. When this is done, the excessive risk … of twin deliveries … largely disappear. At least in women who want two or more children and have no obstetrical contraindications to twin pregnancies, the statistically correct conclusion, therefore, is that the prevention of twin pregnancies with a broadly based eSET policy, likely, does not result in significant risk … reductions for IVF patients … (Gleicher, 2013).

Singleton pregnancies have risks. The combined risks of two successive singleton pregnancies are cumulative. However, the notion that the cumulative complication rate from two individual ART single pregnancies (and deliveries) is similar to that associated with one ART twin pregnancy, the foundation to the proposition that two singleton pregnancies are not safer than one twin pregnancy, is demonstrably false.

It is true that a number of maternal complications (such as gestational diabetes, gestational hypertension, among others) are approximately two to three times more likely with twin compared with singleton pregnancies (Wein et al., 1992; Schwartz et al., 1999; Sibai et al., 2000; Krotz et al., 2002; Buhling et al., 2003; Pinborg et al., 2004a,b; Day et al., 2005; Hernandez-Diaz et al., 2007), suggesting that the risks for one twin delivery may be similar to the cumulative risks for two successive singleton pregnancies. Not all patients having a singleton ART pregnancy desire a second, so for them there is no cumulative risk. But even for those who do, a recent study directly addressed and counters this argument. Complication rates were compared between ART twin births with patients having two consecutive ART singleton births (Sazonova et al., 2013); thus, the total number of children born per parent was equalized between the two comparison groups. This comparison revealed that while the risks of some maternal complications (e.g. gestational diabetes and placental abruption) are equivalent between one twin and two singleton ART births, one twin compared with two singleton ART births is associated with more than twice the risk of pre-eclampsia (14 versus 6%), more than twice the risk of Cesarean section (61 versus 27%) and nearly five times the risk of preterm premature rupture of the membranes (12 versus 2.5%). Other rare but serious maternal complications in mothers carrying twins (e.g. pulmonary edema with an estimated RR of 7 and heart failure with an estimated RR of 13; Walker et al.,
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2004) are also many times more likely in a twin gestation compared with two singleton gestations. Mothers of ART twins reportedly spend an average of 15 days hospitalized in the prenatal ward, compared with only 7 days of prenatal hospitalization for two singleton ART pregnancies (Koivurova et al., 2004). Thus, even among those patients who should seek a second ART birth, maternal complications are not at all equivalent between two ART singleton and one ART twin pregnancy; some are considerably more likely with twins.

In addition to these physical risks, twin deliveries also impose considerable psychological burdens on new parents. Compared with mothers of singletons, mothers of twins experience significantly more post-partum depression and anxiety (Fisher and Stockly, 2003; Choi et al., 2009; Vilksa et al., 2009), and they continue to suffer from increased fatigue, depression and anxiety for many years after delivery (Thorpe et al., 1991; Merenkov, 1995). Fathers of twins also experience more frequent sleeping difficulties and increased symptoms of anxiety, depression and social dysfunction during the first year (Vilksa et al., 2009).

And, importantly, while the assertion of equivalency of maternal risks for one twin versus two singleton ART births may find some adherents, this argument has no validity in the context of risks to the children born following ART treatment. From the perspective of the children, both twins are subjected to much higher risks than each child resulting from singleton pregnancies. The accusation that ‘most published perinatal outcome comparisons between singleton and twin pregnancies are based on spontaneous conceptions’ and that the use of such information ‘greatly exaggerated’ the relative benefits of singletons over twins in the context of ART (Gleicher and Barad, 2009) is not accurate. There is abundant evidence, some of which is summarized below, that directly addresses perinatal outcomes between ART singletons and twins even after the higher proportion of twin pregnancies lost to miscarriage have been excluded. According to US Centers for Disease Control and Prevention (CDC) records of all reported ART cycles performed in the USA, ART twins compared with ART singletons are four-and-a-half times more likely to be born preterm (65 versus 14%), more than six times as likely to be low birthweight (57 versus 9%) and four-and-a-half times more likely to be very low birthweight (8.5 versus 1.9%) (Sunderam et al., 2009). ART twins are six times more likely to be born prior to 32 weeks compared with ART singletons (7.5–8.5 versus 1.2–1.3%) (Pinborg et al., 2004a,b; Sazonova et al., 2013), and children born as ART twins are five times more likely to be small for gestational age (12.4 versus 2.3%) (Sazonova et al., 2013). Consequently to this prematurity and low birthweight, each child born in ART twin pairs compared with ART singletons is more than three times as likely to suffer from respiratory disorders (16.2 versus 4.5%), three times as likely to require assisted ventilation (7.4 versus 2.5%), five times as likely to suffer from respiratory distress syndrome (5.3 versus 1.1%), four times as likely to have jaundice (19.2 versus 4.9%), twice as likely to suffer from sepsis (2.3 versus 1.1%), more than three times as likely to have intracranial bleeding (2.3 versus 0.7%) and five times more likely to be diagnosed with patent ductus arteriosus (1.7 versus 0.35%) (Pinborg et al., 2004a,b; Ombelet et al., 2005; Sazonova et al., 2013). Each ART twin child, compared with an ART singleton, is more than twice as likely to be admitted to neonatal intensive care nursery (56–70 versus 22–25%), and those who are spend nearly twice as long there (20 versus 11 days) (Pinborg et al., 2004a,b; Ombelet et al., 2005). Twin gestation also increases the risks of serious life-long disabilities; for example, ART twins compared with ART singletons are approximately twice as likely to be diagnosed with cerebral palsy (Gromberg et al., 2002; Hvidtjorn et al., 2006; Kallen et al., 2010). And critically, twins born following ART are more than twice as likely to succumb to perinatal mortality compared with singleton children conceived following ART (2.4–2.8 versus 1.1–1.2%) (Ombelet et al., 2005; Sullivan et al., 2012).

The delivery of twins at 29 weeks gestation is, for example, a too common phenomenon in twin gestations, and the consequences to two fetuses delivered at 29 weeks in a twin gestation can be catastrophic and life-long for either or both, should they survive at all. The likelihood of two separate singleton pregnancies both delivering infants at 29 weeks is extremely unlikely. Thus, while proponents of twin pregnancy may emphasize that (some) maternal risks are similar for one twin pregnancy compared with two singleton pregnancies in patients seeking a second birth, this is demonstrably incorrect regarding the children.

Proponents of singleton pregnancy like ourselves are not ‘demonizing’ (Belaisch-Allart, 2007) twin pregnancies nor implying that twin pregnancy per se is an ‘adverse outcome’ (van Wely et al., 2006). We fully (and quite happily) recognize that many twin pregnancies result in two healthy children without significant long-term health problems. However, while we do not take the extreme position that twin pregnancy must be avoided, necessitating mandatory SET in all IVF cycles, it must also be recognized that twin pregnancies undeniably subject children to several times the risk of adverse outcomes as detailed above. We cannot easily dismiss these many increased risks as just ‘mild morbidity’ (Gleicher and Barad, 2013); certainly, the increased risk of perinatal mortality cannot be characterized as such.

Promoting SET

So, rather than just counter the arguments posed about the benefits of twinning, what should we do to further promote SET? How can we answer Faber’s call from 1997 that: ‘the incidence of multiple gestation . . . will continue to increase until infertility specialists, patients, and those paying for the results of these pregnancies agree . . . to modify their behavior. Clinics need to stop gauging their worth by a pregnancy rate, and patients must support clinical decisions that increase the probability of having healthy children’ (Faber, 1997).

Clinics

As a matter of best practices, clinics should fully inform patients about the risk of multiple versus singleton gestation and accept the challenges of improving their individual implantation rates through embryologic advances, blastocyst embryo culture (Papanikolaou et al., 2006) and better cryopreservation (Loutradi et al., 2008; Hong et al., 2009). They should embrace promising methodologies such as advanced preimplantation genetic screening (Ly et al., 2011; Mastenbroek et al., 2011), time-lapse imaging (Chen et al., 2013; Herrero and Meseguer, 2013) and/or metabolomics (Nel-Themaat and Nagy, 2011) if evidence of their worth is forthcoming. In this way, a growing cohort of patients with good prognosis can benefit from SET without compromising pregnancy rates, cumulative per ovum pickup or otherwise. In addition, professional societies and government regulatory bodies should promote safe practices with incentives for single pregnancy and disincentives for multiple pregnancies. Grunfeld, in a mathematical reworking of the 2004 US SART clinic reporting statistics, eliminated triplets as a
success (Grunfeld et al., 2008). This led to new rankings, with ART clinics with the lowest average number of embryos transferred (and consequently the lowest number of triplet pregnancies) being rewarded, and those with a greater average number of embryos transferred (and therefore the most triplets) finding themselves ranked lower. Extension of Grunfeld’s analysis could further incentivize single pregnancies within existing national clinic outcome reporting programs. This is especially important as the public reporting of success rates themselves may contribute to competition between clinics for higher success rates, a factor they perceive as weighing against their lowering the average number of embryos transferred per cycle (Alper, 2004; Grunfeld et al., 2008). (One option to consider in clinic reporting is, within the statistics, to give each singleton pregnancy following eSET a premium valuation of two, give a valuation of one to each twin pregnancy and give a valuation of zero to each high-order multiple pregnancy. Clinics would be thus incentivized to maximize the potential for singleton pregnancies, and to improve their patients’ chances of success using SET.) As Land and Evers artfully stated that ‘the percentage of eSETs performed by a par-
ticular assisted reproduction treatment centre does reflect its quality: the ultimate outcome measure of efficacy and safety. Therefore, the eSET rate is the most relevant qualifier of performance in assisted repro-
duction’ even if all transfers are not single (Land and Evers, 2004).

**Payors**

Government support for assisted reproduction should be expanded to more jurisdictions as it has proven to be not only good social policy but sound fiscal policy. As Chamber’s concluded in supporting SET, ‘funding arrangements for ART not only affect who can afford to access ART treatment, but also have the potential to alter the health outcomes of children born as a result. For the sake of the health of children born following ART, we should be asking: “Can we afford not to fund it?”’ (Chambers et al., 2011).

When no government benefit exists, insurance companies should be lobbied with the data showing the benefit to them of reducing the fiscal burden of complicated maternal and neonatal courses, and perhaps life-
long care, in return for clinically appropriate limitations on the number of embryos for transfer.

**Patients**

Patient education and educational materials need to be provided as part of truly informed consent using up-to-date literature and demonstrating the perinatal morbidity and mortality as well as maternal physical, psychological and financial burdens of twin gestation. In that way, patients have the tools to participate in timely decisions on the number of embryos for transfer that promote the birth of a healthy child following ART (van Peperstraten et al., 2008a,b).

**Conclusion: two steps forward, do we take one step back?**

eSET offers exactly the kind of treatment outcome clinicians, typically, try to avoid: a very questionable treatment benefit (i.e. highly questionable reduction of risks) but an obvious negative treatment effect (i.e. reduction in immediate pregnancy chances). eSET, therefore, does not, as has been widely suggested, represent the logical next step (Gleicher, 2013).

We disagree with the basis for, and the conclusions promulgated by the quotation above. We thought the challenge ahead for ART professionals would be to further increase successful implantation rates through patient and embryo selection and to provide patients the data demonstrating the benefits to limiting the number of embryos for transfer. Instead, we are compelled to counter untenable campaigns to delegiti-
mize the goals of a singleton birth. But if we provide the cogent, data derived counter-arguments, perhaps we can return to the relevant clinical tasks ahead, so patients may be able to alleviate their infertility with a safe, healthy outcome and family. As had been so clearly stated by the ESHRE Consensus Conference (Land and Evers, 2003), and echoed in the 2012 ASRM Practice Committee report, Elective single-

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