Review

Why and how should multiple pregnancies be prevented in assisted reproduction treatment programmes?

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Abstract

Although most professional societies have issued guidelines to diminish the number of embryos to be transferred during assisted reproductive techniques, the incidence of multiple pregnancies remains unacceptably high. The burden of morbidity and mortality seems to increase substantially with each fetus in a multiple gestation. As a result, there has been growing debate on the need to prevent multiple pregnancies. The infertility specialists who can solve the infertility problem are usually shielded from the complications of multiple pregnancies. If they were involved in the delivery and, more particularly in the care of multiple pregnancies (both financially and socially), their attitude would probably change. IVF centres should gradually reduce the mean number of embryos per transfer in terms of the cost:benefit ratio. A further reduction to one single embryo per transfer in good cases would be similarly acceptable. Laboratory expertise is of vital importance, especially in terms of embryo culture, embryo selection, and freezing and thawing techniques in embryo transfer programmes for reducing the number of transferred embryos.

Keywords: *adverse outcome, ART, embryo transfer, multiple pregnancy, ovulation induction*

Should multiple pregnancies in assisted reproduction programmes be prevented? Why? How?

Multiple pregnancies are known as the most severe complication of ovulation induction therapies and assisted reproductive technologies, resulting in considerable medical risks for the mother and offspring, as well as excess obstetric and neonatal costs. In most IVF programmes, the incidence of multiple pregnancy varies between 20 and 30% despite the technological developments in assisted reproduction (Lynch *et al*., 2001; Koivurova *et al*., 2002).

In many countries, more than 2% of newborns have been reported to be born after assisted reproductive treatment [European Society of Human Reproduction and Embryology (ESHRE), 2002], among those, a 20-fold increase in multiple pregnancies compared with spontaneous pregnancies has been encountered (Ozturk *et al*., 2001). Within this context, the importance of multiple pregnancy in IVF practice is becoming prominent.

The reason behind the tendency to increase the number of embryos transferred seems to be the fear of causing a reduction in current pregnancy rate. Parallel to this, the traditional emphasis has been on the transfer of multiple embryos in order to boost success rates, but the ideal treatment procedure should combine quantity (rate of pregnancy) with quality (healthy singletons).

Laboratory expertise is of vital importance, especially in terms of embryo culture, embryo selection, and freezing and thawing techniques in embryo transfer programmes for reducing the number of transferred embryos.

Correct counselling is also very important since it is known that sometimes infertile couples desire multiple pregnancies (Gleicher *et al*., 1995). Patients focus solely on pregnancy and pay little attention to the adverse outcomes of this. It is likely that such couples are not really aware of the real risks associated with multiple pregnancies. When women were presented with scenarios of the differing pregnancy-associated risk magnitudes between single and multiple pregnancies, their desire for twin pregnancy was reported to decrease (Grobman *et al*., 2001). This means that good counselling should include realistic information, not only on the risk of twin gestation but also on later burdens with multiple births. While opinions regarding the acceptability of a twin pregnancy as one of the normal outcomes of assisted reproduction may vary, twins are associated with a five-fold increased risk of perinatal mortality, morbidity and long-term health problems when compared with singletons (Dhont *et al*., 1999). This inevitably aggravates the emotional burden on parents and leads to increased costs for them as well as for health service providers.

Embryo transfer and multiple gestations

Most IVF centres reject the idea of replacing only one embryo because they fear it will reduce success rates. On the other hand, although transfer of a single embryo in every patient would certainly cause a dramatic fall in overall pregnancy rates, a specific subgroup of patients at risk for multiple gestation would benefit from this even with current IVF techniques. It is therefore necessary to consider an individualized embryo transfer policy: elective transfer of a single embryo (eSET) in patients at risk for multiple gestation, and a more liberal attitude for those with a less good prognosis. This would significantly reduce the number of multiple gestations without a dramatic fall in overall success rates. The larger the subgroup with good prognosis, the more multiple pregnancies would have been avoided by eSET, but the greater the impact would have been on the overall pregnancy rate. Therefore, the selection of the patients to receive one embryo should be made properly, in order to keep a balance between reduction in multiple gestation and effect on overall pregnancy rate.

Perinatal morbidity and mortality

Multiple pregnancies are associated with unfavourable maternal, obstetric, perinatal and neonatal outcomes. Multiple pregnancy is an important risk factor for preterm delivery and low birth weight and many of the perinatal complications are caused by these factors. The burden of morbidity and mortality seems to increase substantially with each additional fetus in a multiple gestation. According to data from the National Vital Statistics Report for the USA in 2001, the gestational age at birth was reduced by three weeks for every additional fetus, while the birth weight of the average triplet was approximately half of that for the average singleton (**Table 1**) (Martin *et al*., 2002).

Multiple pregnancies conceived by assisted reproduction are associated with a higher perinatal morbidity and mortality (Wang *et al*., 1994; Tallo *et al*., 1995; Doyle, 1996; Chitrit *et al*., 1999). Stillbirths, early neonatal deaths, late neonatal deaths, and infant mortality are higher in multiple pregnancies and the rates increase with the number of fetuses. Data from an English study showed that multiple births represented only 2.5% of all births but they accounted for 8% of all stillbirths, 19% of all neonatal deaths and 7% of all post-neonatal deaths in 1991 (Doyle, 1996). Neonatal death was the most evident factor affected by multiple pregnancies, with a rate seven times higher in twins and 20 times higher for triplets and higher-order pregnancies. It has been shown that for multiple pregnancies, the percentages of intrauterine growth retardation, intrauterine fetal death, low birth weight (less than 2500 g) and very low birth weight (less than 1500 g) were significantly higher and significantly more neonates were admitted to the neonatal intensive care unit with necrotizing enterocolitis, respiratory distress syndrome, intraventricular haemorrhage and premature retinopathy (Rizk *et al*., 1991; Tan *et al*., 1992; Callahan *et al*., 1994; Causio *et al*., 1995; Gardner *et al*., 1995; Olivennes *et al*., 1996; Moise *et al*., 1998; Daniel *et al*., 2000).

In a recently published study it was shown that the infant mortality rate was higher in multiple pregnancies, 6.1 per 1000 live births for singleton pregnancies and 31.1 for multiple pregnancies, (Russell *et al*., 2003). A large population-based cohort study of over 1,000,000 births in Australia and USA, of which more than 20,000 were twins, found that twins had an approximately five-fold increase in the risk of fetal death when compared with singletons, and the risk varied between twin

pregnancies, with second-born twins, twins from same sex or growth discordant pairs, and twins whose co-twin died *in utero* having an increased risk of death (Scher *et al*., 2002; Kahn *et al*., 2003). Growth concordance *in utero* is considered a reassuring sign in twins and conversely, discordancy is thought to possibly reflect a hostile intrauterine environment at least to the smaller twin. Consequently, increased surveillance of discordant twins is commonly practised. Monochorionic twins are at further risk for type-specific perinatal complications, for example twin–twin transfusion syndrome (Sherer, 2001).

Long-term medical and developmental problems

Prematurity and low birth weight are the two main determinants of perinatal mortality and handicap. In particular, the risk of neurological impairment is higher in multiple pregnancies than in singletons. The risk of handicap increases with the number of fetuses. Twins have been shown to have a 1.4-fold increase in risk for all handicap while the risk for triplets is two-fold higher for all handicap compared with singletons (Luke and Keith, 1992). Cerebral palsy is an important neurological impairment and its incidence increases with additional fetuses. Twins were found to have an odds ratio of 10.2 of having cerebral palsy compared with singletons (Petridou *et al*., 1996). Mental and language development may also be impaired in multiple pregnancies (Hay *et al*., 1987; Williams *et al*., 1996).

The rate of malformation is increased in multiple gestations. For example, specific malformations (neural tube defects and structural malformations of the gastro-intestinal tract) have been found to be increased in twin pregnancies (Kallen, 1986; Doyle *et al*., 1991; Mastroiacovo *et al*., 1999). Moreover, in monozygotic twins, congenital anomalies occur in a higher rate, both in live-born babies and miscarriage (Little and Bryan, 1988; Cameron *et al*., 1983).

Maternal morbidity and mortality

Maternal morbidity and mortality are increased in multiple pregnancies (among which twins represent a large majority) as demonstrated in a review (Senat *et al*., 1998). The risk of death is three times higher in multiple pregnancies (Senat *et al*., 1998; Olivennes 2000).

Hypertensive disorders, thromboembolism, urinary tract infection, anaemia, utero-vaginal bleeding (placental abruption, placenta praevia) and complications related to tocolysis are greater, and, as a result of these complications, the hospitalization rate is higher in multiple pregnancies. For example, for hypertension, a major complication of pregnancy, the odds ratio in mothers of twins varies from 1.8 to 3.4, according to different published studies (Senat *et al*., 1998; Olivennes, 2000; Strauss *et al*., 2002). The risk of post-partum haemorrhage is 3–4.5 times higher in multiple pregnancies too. Multiple pregnancy is an independent factor, and has a 2.3 odds ratio, for a woman to be admitted in an intensive unit.

Economic analysis of multiple pregnancies and neonatal costs

The complications of multiple gestations may have significant economic implications both for the family involved and for the healthcare system. Therefore, quality control systems for the reduction of multiple pregnancies would reduce both medical complications and the psychological effects on the family, leading to decreased costs.

Multiple pregnancies are associated with a high rate of hospitalization because of the maternal complications (hypertension, thromboembolism, urinary tract infection, uterine bleeding from placenta praevia etc) and women with multiple pregnancies are also more likely to require long periods of bed rest, hospitalization, surgical procedures such as cervical cerclage, tocolysis for premature labour and emergency Caesarean section.

Approximately 500,000 IVF/intracytoplasmic sperm injection (ICSI) cycles are performed in the world each year (Nygren and Nyboe-Andersen, 2002). These result in ~100,000 ongoing pregnancies; a large number of the children resulting from these are part of a set of twins or higher-order multiple births. If the global incidence for post-IVF/ICSI twinning is assumed to be 25% and for higher-order multiples to be 3%, these ~100,000 ongoing pregnancies will result in 72,000 singletons, 50,000 twin children and 9000 triplet children for a total of 131,000 children. Multiple gestations result in higher perinatal healthcare costs, initially as a consequence of premature delivery and neonatal intensive care, drug therapies and diagnostic procedures (Papiernik, 1991; Centers for

Table 1. Gestational age and birth weight characteristics by plurality. Data from the National Vital Statistics Reports for the USA for 2001 (Martin *et al*., 2002).

	Singletons	*Twins*	*Triplets*	*Quadruplets*	*Quintuplets*
Number	3,897,216	121,246	6885	501	85
Gestational age (weeks)					
<32 (%)	1.6	11.8	36.7	64.5	78.6
<37 (%)	10.4	57.4	92.4 97.8	91.7	
Mean (SD)	38.8 (2.5)	32.0 (4.0)	35.4 (3.7)	29.6 (4.1)	29.1 (3.9)
Birth weight (g)					
<1500 (%)	1.1	10.2	34.8	68.4	77.4
<2500 (%)	6.0	54.9	94.0	98.4	91.7
Mean (SD)	3339(573)	2353(647)	1678(574)	1290(549)	1269(676)

SD = standard deviation.

Disease Control and Prevention, 2003). Assuming an incidence of ~10% of severe complications and sequels per child belonging to a set of twins or higher-order multiples (Wennerholm and Bergh, 2000), this means that each year IVF/ICSI alone is responsible for ~6000 severely disabled children worldwide. In addition, non-IVF treatments are responsible for at least a similar number of multiple births. Apart from severe complications such as cerebral palsy, there are other physical and mental complications, as well as non-medical problems, such as educational, emotional, (neuro)linguistic, financial, familial and sexual consequences that usually accompany the raising of twins (Dhont *et al*., 1999).

Multifetal pregnancy reduction

The keyword here is prevention (Nisand and Shenfield, 1997). If multiple pregnancies can be prevented by reducing the number of embryos replaced, than this should be preferred to multifetal pregnancy reduction (MPR). A number of people may find it very difficult to accept that doctors first create a problem and then solve it by another medical intervention. Multifetal reduction is ethically acceptable if the physician has done what he should to prevent the occurrence of the multiple pregnancy.

There is evidence showing that MPR can prolong gestation of the remaining fetuses and so reduce the risks of early preterm delivery. Reduction of triplet pregnancies to twins increases gestation by 2–3 weeks, and reduction to twins or a singleton from higher-order pregnancies prolongs the pregnancy even more (Stone *et al*., 2002; Strauss *et al*., 2002; Rochon and Stone, 2003). However, MPR, like any invasive procedure, can lead to unintended loss of the entire pregnancy. In the studies by Stone, 1000 consecutive cases were evaluated and the pregnancy loss rate before 24 weeks was 5.4% (Stone *et al*., 2002); 15% of these cases occurred within 4 weeks of the procedure, but more than half occurred after 8 or more weeks following the MPR.

When the medical risks associated with the procedure and the high ethical and psychological stress for the couple are weighed against the disadvantages of not being pregnant in that cycle, then the balance tips in favour of trying to become pregnant again in a later cycle.

The risks of multifetal pregnancies are significant. Therefore, evidence-based counselling of couples seeking treatment for infertility and prevention of high-order multiple pregnancies through the prudent use of reproductive techniques attains paramount importance.

ESHRE, WHO and ASRM recommendations

The conclusion of the consensus meeting of the European Society of Human Reproduction and Embryology (ESHRE, 2002), was that 'the essential aim of IVF/ICSI is the birth of one single healthy child'; in other words, the meeting's recommendation was that the outcome measure of assisted reproductive technology and non-assisted reproductive technology should be singleton live birth rate and eSET has been recommended in a first or second IVF/ICSI cycle in women below 36 years of age, if at least one good quality embryo is available (Land and Evers, 2003).

The World Health Organization (WHO) recommended in 2001 that 'no more than two embryos be transferred per cycle' (Vayena *et al*., 2001).

The American Society for Reproductive Medicine (ASRM) guidelines recommend: 'transferring a maximum of two embryos for age <35, when there are at least three "improved" quality embryos and excess embryos available for cryopreservation; transferring a maximum of three good quality embryos for age <35, when there are no more than three good quality embryos with none available for cryopreservation; transferring a maximum of four embryos for age 35 to 40; and transferring a maximum of five embryos for age 40 and above, or four multiple failed cycles' (American Society for Reproductive Medicine, 1999).

Single versus double embryo transfers

A report of the ESHRE Campus Course (2001) showed per cycle clinical pregnancy rates for eSET equal to rates for elective double embryo transfer(eDET).

In contrast to those findings, the US national IVF clinic results for 2001, provide unequivocal evidence that birth rates for eSET are significantly lower than for eDET, and also that birth rates are not increased when more than two fresh non-donor embryos are transferred (Centers for Disease Control and Prevention, 2003). The live birth rate per transfer, for patients with the most favourable prognosis, because of being aged below 35 years with extra embryos cryopreserved for future use, was 30.0% for eSET and 51.7% for eDET. The live birth rate for all transfer cycles, performed during 2001 in the US, was 11.3% for SET and 37.2% for DET. When three, four or more than four embryos were transferred, the live birth rate was less than 47% for patients with the most favourable prognosis, and less than 35% for all patients. These results indicate that, if SET had been mandatory, the live birth rate for patients with the most favourable prognosis would have been reduced by 42%. On the other hand, the primary purpose should be the birth of a single healthy child.

Multiple pregnancies with increased neonatal mortality and child handicap could be overcome if a single embryo of known developmental competence could be selected precisely (Vilska *et al*., 1999; Martikainen *et al*., 2001; Tiitinen *et al*., 2001). Reliable markers for embryo selection are embryo morphology (Scott *et al*., 1991; Staessen *et al*., 1992; Alikani *et al*., 1999), development rate (Staessen *et al*., 1992; Ziebe *et al*., 1997; Salumets *et al*., 2002) and the presence of multinucleated blastomeres (Pelinck *et al*., 1998). In addition, some other criteria may be helpful for the selection of viable embryos at the zygote stage (Scott and Smith, 1998; Tesarik and Greco, 1999). Early cleavage of zygotes occurring by 25–27 h after insemination or ICSI could be used to predict the implantation potential of embryos (Edwards *et al*., 1984; Shoukir *et al*., 1997; Sakkas *et al*., 1998, 2001; Salumets *et al*., 2003). In some studies, amino acid turnover has been shown to be a non-invasive parameter for the selection of competent embryos (Houghton *et al*., 2002).

Limiting the number of embryos transferred by eSET would reduce triplet and higher-order births from all causes by 42%, but would reduce total twin births by no more than 12%, and some twin births due to IVF would still occur because of monozygotic splitting. Limiting the number of embryos transferred to two by eDET would also eliminate 42% of triplet births, and the number of twin births due to IVF would be decreased by approximately 20%, by eliminating twin births that begin as triplet and higher-order gestations (Dickey *et al*., 2004).

The efficacy of SET and DET was compared in a prospective study with the first cycle of patients. In the first study, patients <34 years of age with >2 top quality embryos were randomized to SET or DET; 26 SET resulted in 17 conceptions, 14 clinical and 10 ongoing pregnancies (implantation rate (IR): 65.4%; ongoing pregnancy rate (OPR): 38.5% with one monozygotic twin). Twenty-seven DET resulted in 20 ongoing conceptions with six (30%) twins (IR: 48.1%; OPR: 74%). It was concluded that, by using SET and strict embryo criteria, an OPR similar to that in normal fertile couples can be achieved after assisted reproduction treatment, while limiting the dizygotic twin pregnancy rate to its natural incidence of <1% of all ongoing pregnancies (Gerris *et al*., 1999). In another randomized study, a total of 144 women, who had had at least four good quality embryos available after IVF/ICSI and who had no more than one previous failed treatment cycle, were randomized to have either one or two embryos transferred. The treatment outcomes including those after frozen embryo transfer were compared between these groups. The clinical pregnancy rate per transfer was 32.4% in the one-embryo transfer group and 47.1% in the two-embryo transfer group, the difference being not significant. Eleven twin deliveries occurred (n = 39) in the two-embryo transfer group and there was one pair of monozygotic twins in the one-embryo transfer group (Martikainen *et al*., 2001).

Some assisted reproduction treatment singletons and twins are caused by spontaneous reduction from higher-order gestations

Singletons and twins produced after assisted reproduction treatment are not all originally singletons and twins; some of them are caused by spontaneous reduction from higher-order gestations. A retrospective analysis of multiple pregnancies, diagnosed by ultrasound before the seventh week of gestation, found that 47% of triplet gestations and 35% of quadruplet gestations had undergone spontaneous reduction or had lost fetal heart activity by the 12th week of gestation, and were continuing as visible singletons or twins (Dickey *et al*., 2002). Additional analysis showed that 15% of singleton births and 19% of twin births following IVF began as higher-order gestations (Dickey *et al*., 2002). Singleton births following IVF that began as single, twin, triplet and higher-order gestations were born 1.8 days, 5.0 days, and 12.4 days earlier, respectively, compared with spontaneous singleton births that began as single gestations. Twin births due to IVF, that began as twin, triplet and quadruplet or higher-order gestations were born 2.7 days, 6.2 days, and 18 days earlier, respectively, compared with spontaneous twin births that began as twin gestations. In the absence of spontaneous reduction from higher-order gestations, the proportion of singletons due to IVF, born before 32 weeks, was not increased compared with spontaneously conceived singletons (1.1 versus 1.3%). Similarly the proportion of premature twins was only slightly increased (10.4 versus 9.5%) compared with spontaneously conceived twins.

The increased incidence of premature birth reported for IVF singleton and twin births, compared with spontaneous pregnancies, is partly due to the singletons and twins originating from the higher-order gestations, and because of this it is necessary to re-evaluate the outcome of IVF births that follow transfer of two embryos.

Multiple pregnancies after ovulation induction and enhancement

There is not any system for recording the ovulation induction or ovulation enhancement procedures and exact statistics for multiple pregnancies attributable to these therapies are not available. Also, there are no guidelines or restrictions for them.

The available evidence suggests that at least one-third of twin pregnancies and the majority of triplet or higher-order gestations can be attributed to ovulation-induction procedures (Levene *et al*., 1992; Norwitz, 1998; Tur *et al*., 2001).

The increased risk of multiple pregnancies through ovulation induction can be decreased by switching patients to IVF treatment, by reducing the number of follicles or by cancelling the treatment cycle

Discussion

One of the main challenges in assisted reproductive treatment programmes is to avoid multiple pregnancies without there being a significant decrease in the overall pregnancy rate. A lot of scientific papers have been published on the technical aspects of the IVF procedure but few studies have addressed the issue of the perinatal outcome of multiple pregnancies and of the children's development and well-being.

Many infertility specialists are unwilling to reduce the number of embryos transferred because they fear it will reduce the success rate. But it is unacceptable to say 'We achieved the pregnancy, it was great, but, the children are handicapped and the family suffers from depression'.

Increasing the number of transferred embryos in patients with less good prognosis is accepted by most infertility centres as a routine procedure and several studies have been published on this subject (Azem *et al*., 1995; Adonakis *et al*., 1997). However, increasing the number of embryos transferred does not increase the chance of a birth, but it does increase the chance of multiple births (Engmann *et al*., 2001). This is not the case for the reduction to one single embryo per transfer in patients with good prognosis, although the rationale behind this policy is exactly the same.

It has been shown that triplets can nearly be avoided by replacing two embryos without significantly decreasing the overall pregnancy rate (Staessen *et al*., 1993; Templeton and Morris, 1998). However this policy does not prevent twin

pregnancies. The elevated rate of pregnancy complications and neonatal morbidity among IVF children is mainly due to the increased proportion of multiple pregnancies and partly due to maternal characteristics regarding infertility (Koivurova *et al*., 2002). This is also true in twin pregnancies. The need to prevent twin pregnancies is widely accepted, although transfer of two embryos is standard policy in many IVF centres.

The key issue is whether it is ever acceptable to risk the prospect of multiple births by transferring more than one embryo, and what should influence the decision to transfer one, two or more embryos? SET for all patients is not widely accepted. IVF centres should gradually reduce the mean number of embryos per transfer in terms of the cost:benefit ratio. A further reduction to one single embryo per transfer in good cases would be similarly acceptable.

Laboratory expertise is highly important in the selection of embryos for transfer. Several criteria may be used to identify the best quality embryos, and it is likely that the use of a combination of various scoring criteria throughout preimplantation development will lead to a higher chance of identifying the most viable embryo for transfer.

The cleavage stage, degree of fragmentation and absence of multinuclear blastomeres are important (Pelinck *et al*., 1998; Van Royen *et al*., 2001); early cleavage, also, seems to be a strong indicator (Edwards *et al*., 1984; Shoukir *et al*., 1997; Sakkas *et al*., 1998, 2001; Salumets *et al*., 2002, 2003). Several embryo scoring systems are available for predicting pregnancy, (Terriou *et al*., 2001) but the most appropriate embryo scoring system might be established by eSET. Another important point is that the policy of limiting the number of embryos transferred is not possible without a good cryopreservation programme. When elective embryo transfer is combined with freezing of extra embryos for later use, the cumulative delivery rate per oocyte retrieval can be high. The use of preimplantation genetic diagnosis offers the possibility of identifying and transferring only embryos that are chromosomally normal and may make single embryo transfer practical in future.

Embryo quality is the most important single factor predicting pregnancy and birth rate. Meanwhile, the other factors should be evaluated for the individualization of transfer strategy too. For example, age of the patient, basal FSH level, ovarian response to stimulation, number of mature oocytes and endometrial receptivity are other important factors. An expert meeting on infertility therapy-associated multiple pregnancies was held in 2003, in New York (Bertarelli Group, 2003). It was devoted to the use of debates and reached the following conclusions:

" – Patients deserve and require all available information a priori. – On-line prospective data reporting must include: (i) cumulative singleton live birth rates per retrieval; (ii) the proportion of cancelled cycles; (iii) SET, DET and blastocysts; (iv) live twin and triplet birth rates (v) embryo reduction data where applicable; (vi) frozen embryo data if applicable. – With improved technology which has augmented the pregnancy potential of pre-embryos with better selection techniques, and for other reasons, there comes the recognized need to update current embryo transfer guidelines in order to reduce the incidence of high-order and twin gestations. – Embryo reduction is an unacceptable solution to the multiple gestation challenge, but remains unavoidable in certain high-risk cases. – An active and effective freezing programme is essential for reducing or preventing altogether the occurrence of infertility therapy-associated multiple gestations, as well as other complications affecting patients' health."

The Conference statement from the meeting (Bertarelli Group, 2003) was as follows:

"– 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 psychological and financial challenge to couples and their children as well as society as a whole. – The incidence of IVF-associated triplets is plateauing or declining, whereas twin pregnancies continue to increase. – Infertility therapy-associated multiple gestations remain a challenge worldwide. The substantial contribution of ovulation induction and ovulation enhancement regimens remains a largely unattended, major challenge. – Preventing, altogether, the occurrence of infertility therapy-associated triplets must be viewed as an initial goal. Reducing the incidence of twin gestation is viewed as a follow-up goal. – Further progress towards reducing the incidence of IVF-associated twin pregnancies would require additional comparative prospective studies of the impact, if any, of SET versus DET on the live-birth rate. Improved means of assessing embryo quality and uterine receptivity remains an ongoing challenge. – The quality of an IVF programme is to be measured by its ability to maximize the singleton birth rate, rather than by its overall pregnancy rate."

The current authors fully support these conclusions.

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