Chapter | 7

Health economics of two IVF treatment strategies

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Submitted

Introduction

The increasing success of IVF in the 1990s lead not only to an increased pregnancy rate, but also to an increase in the incidence of multiple births(6). Several cost studies have demonstrated the impact of multiple births on health care resources (16,37,201). The standard IVF regimen with the transfer of two embryos has a inherent high probability of multiple pregnancies, resulting in high costs due to intensive antenatal surveillance, increased chances for complications of both mother and child, hospital admissions, and perinatal and post partum care (37,56,55). The financial burden of multiple births on health care resources has been calculated to be greater than the costs of IVF treatment itself (216). There is a growing awareness that the high rate of multiple pregnancies can be greatly reduced by a single embryo transfer (SET) policy (217,43,6). However, single embryo transfer results in a lower live birth rate per cycle(218,43). There is a clear need for the further evaluation of efficacy and economic consequences of SET.

The introduction of gonadotropin-releasing hormone (GnRH) antagonists into clinical practice has enabled the development of novel milder ovarian stimulation protocols (111). Mild stimulation might be advantageous when evaluated over an entire (multiple cycle) treatment period, since the amount of time needed to complete a single IVF cycle is reduced, the costs of stimulation are lower (26,112) and the patient drop out rate may decrease. Mild treatment strategies with SET may result in more IVF cycles in the same period of time and therefore result in a similar term live birth rate per treatment period compared with standard stimulation protocols with the transfer of 2 embryos (41). Such a mild treatment strategy may also reduce costs by eliminating multiple pregnancies. As reported previously, a mild treatment strategy in IVF (mild ovarian stimulation with GnRH antagonist co-treatment and SET) results in similar cumulative term live birth rates within one year compared with a standard treatment strategy ("long" ovarian stimulation protocol, including GnRH agonist co-treatment and transfer of 2 embryos) in women less than 38 years of age, while greatly reducing multiple pregnancy rates (163).

Recently published randomised trials comparing the costs of single and dual embryo transfer (201,219), differed from our study in that costs were calculated per cycle and both groups were stimulated with the standard long protocol. Other cost studies comparing single and dual embryo transfer were not randomised controlled trials, but were based on theoretical extrapolations or decision-analytic calculations and were mainly based on one IVF cycle (35,54,55). These studies suggested lower costs for SET. The aim of this paper is to provide detailed information concerning the economic consequences of two different treatment strategies including ovarian stimulation protocols and embryo transfer policies during consecutive treatment cycles.

Methods

Study design

The study protocol was approved by the ethics review board of both participating University Medical Centers (Utrecht and Rotterdam). Patients with an indication for IVF or Intracytoplasmic Sperm Injection (ICSI) treatment in two academic medical centres were recruited in the period February 2002 through March 2004 (205). Patients with a regular indication for IVF or IVF/ICSI (tubal, male, unexplained), female age < 38 years, normal menstrual cycle (cycle length between period 25-35 days) and without severe obesity or underweight (body mass index 18-28 kg/m^2) were eligible for the study. Patients were randomly assigned to undergo either mild stimulation with GnRH antagonist co-treatment combined with single embryo transfer (mild strategy) or a 'standard' ovarian stimulation protocol where pituitary down regulation was established using a GnRH agonist long-protocol combined with dual embryo transfer (standard strategy). In order to compensate for a possible reduction in pregnancy rate per cycle, patients in the mild treatment group were offered an extra reimbursed treatment cycle on top of the three cycles reimbursed at that time in the Netherlands. It was considered that 12 months after commencing treatment, 3 cycles of standard IVF would be feasible for most couples, while 4 mild strategy cycles would be possible in the same period of time, due to the shorter duration and lower psychological burden. The study design has been described in great detail previously (205).

The primary endpoint for this study was defined as total costs of IVF treatment per couple within 12 months after randomisation, including costs of resulting pregnancy and postnatal costs of the mother and the infant(s) up to six weeks after the expected day of delivery. Since cumulative ongoing pregnancy rates within one year resulting in term live births were almost similar for both treatment groups (44.7% in the standard treatment group versus 43.4% in the mild treatment group) (220), the economic evaluation in the current analysis is primarily designed as a cost-minimization analysis (CMA).

Cost calculations

The costs of the two IVF strategies were assessed in two stages. Firstly, the cost of IVF treatment itself, starting with the first IVF cycle and ending with the outcome of the last IVF-cycle within one year (pregnant, no pregnancy or drop out). Secondly, the cost of antenatal, peripartum and post partum care were analysed in women who became pregnant after IVF treatment.

Medical costs were calculated by multiplying the volumes of health care use with the corresponding unit prices. The costs of IVF treatment were distinguished into medical costs in the hospital (intramural), extramural medical costs, and non-medical costs. Medical costs in the hospital consist of scheduled and unscheduled outpatient visits, number of IVF cycles, personnel time per cycle, use of GnRH analogues and recombinant FSH, costs of ultrasound and hormonal monitoring, the embryo transfer procedure and costs associated with complications. Extramural medical costs consist of general practitioner (GP) consultations, and social worker. Non-medical costs are associated with travel and absence from work/sick leave due to the treatment or associated complications. Cost volumes in the treatment stage were recorded with case record forms (CRFs), hospital-based management and budgetary information systems, patient questionnaires and literature (Figure 1).

The costs of pregnancy and obstetric care were distinguished into medical costs in the hospital (secondary obstetric care) and medical costs outside the hospital (e.g. primary obstetric care, GP care, etc.). Pregnant patients received several questionnaires regarding health care use each covering three month periods of their pregnancy. The final questionnaire covered the period around the calculated term date, until 6 weeks

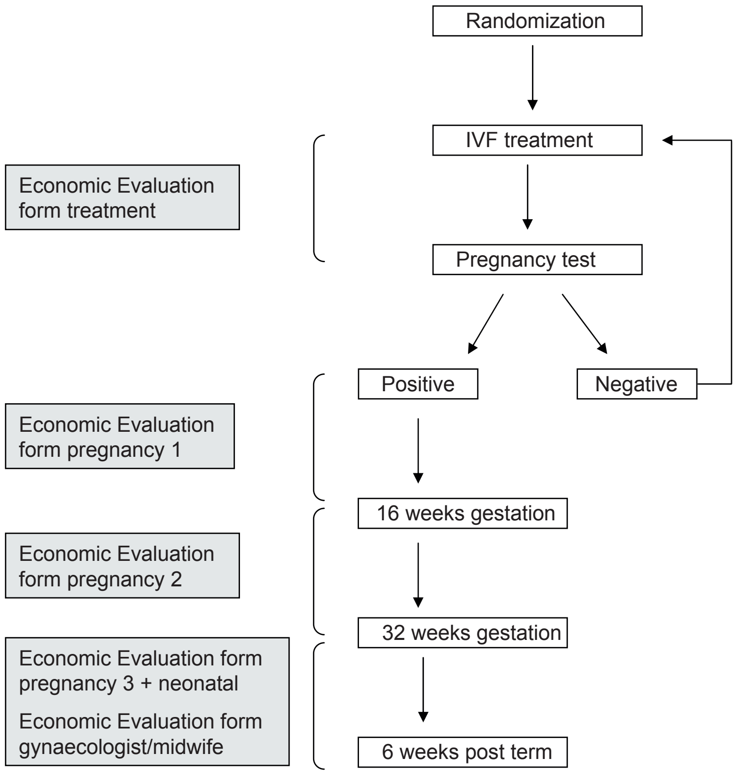

Figure 1. Flow chart of the economical evaluation measure points

thereafter. This means that the neonatal costs are covered for a 6-week period post-term. For pre-term births, the postnatal period is therefore longer and costs higher than for term births (189). In order to receive medical information regarding birth, questionnaires were sent to the responsible obstetrician.

For the most important cost items, unit prices were determined by following the micro-costing method (221), which is based on a detailed inventory and measurement of all resources used. During the determination of unit prices 2 embryos were transferred in the majority of cycles. Therefore all unit prices are determined for the transfer of 2 embryos. The calculation of the unit price of the IVF treatment consisted of detailed measurement of investments in manpower, equipment, materials, housing and overhead. The salary schemes of hospitals and other health care suppliers were used to estimate costs per hour for each caregiver. Taxes, social securities and vacations were included, as well as the costs of the time that could not be assigned to other patients. The costs of equipment included those of depreciation, interest and maintenance. Costs for inpatient days in hospital were calculated from real, basic costs per day using detailed information from the financial department of the hospital. For the unit price per inpatient day in hospital, a distinction was made between general and university hospitals. These estimates included overhead and indirect costs. Other charges assaulted with inpatient and outpatient care were derived from previous publications (188), in order to make our results more comparable with other research and to make these unit costs independent from the specific hospital prices. For these items we used charges as a proxy of real costs. In the Netherlands a 'fee for service' system is used for the remuneration of medical interventions and diagnostic procedures. In order to calculate the costs for medication, we used pharmacotherapeutic charges. Costs caused by loss of economic productivity due to absence from work were also taken into account, using charges (188). Table 1 gives an overview of the cost categories and data used in the cost calculations.

Statistical analysis

Analysis was carried out according to the intention-to-treat principle. For an effectiveness trial, the focus should not be the cost per cycle but rather the overall cost that a patient may expect over a given treatment period (including cryo cycles) (105). Therefore we elected to base the analysis on a one year treatment period, which would allow the treatment strategy that is best tolerated by the patients and requires the least amount of time per cycle, to realize more chance of success than the other strategy. We used the Kaplan-Meier method, in which it is assumed that dropouts who do not wish to receive any more treatment have a zero chance of the outcome, i.e. a realistic assumption (no censoring) (107). The time period of analysis started from the moment of randomisation, to avoid post randomisation selective dropout.

Missing cost items arising due to non-response to the questionnaires were imputed, and stratified by randomisation arms to avoid the loss of data. For this purpose, the AregImpute method in S-plus (MathSoft. Inc., Seattle, WA, version 2000 was used). A comparison of the costs between both treatment strategies was performed with the independent groups t-test.

Table 1. Cost categories and data used in cost calculations

Cost category	Parameter	Data collection volume of care			Cost estimate *(unit price)*
		CRF (physician)	*Questionnaires patient*	*Questionnaire obst/gyn*	
Technical procedures					
Punction	Strategy	*			Real costs
Laboratory	Strategy	*			Real costs
Embryo transfer	Strategy	*			Real cost
Intramural care					
Hospital (academic)	Days	*	*	*	Real costs
Hospital (general)	Days	*	*	*	Real costs
NICU/MCU	Days	*	*	*	Real costs
Physician (academic)	Visits	*	*	*	Charges
Physician (general)	Visits	*	*	*	Charges
Echoscopy	Number	*		*	Charges
Prenetal research				*	Charges
Other therapy	Number			*	Charges
Delivery	Category		*	*	Literature
Medication					
GnRH	Strategy	*			Cost price
FSH	Days	*			Cost price
HCG/Progesteron	Days	*			Cost price
Extramural care					
Obstetrician	Visits		*	*	Charges
General practitioner (inpatient)	Number		*		Fees
General practitioner (home visit)	Number		*		Fees
Social worker	Number		*		Charges
Maternity nurse	Days		*		Charges
Non-medical costs					
Travel costs	Distance		*		Guidline
Absence from work	Days		*		Guideline

Results

Patient characteristics and clinical outcomes

404 patients were included in the study (Table 2). The mean number of started cycles within 1 year was 2.3 in the mild and 1.7 in the standard treatment group (p < 0.001, t-test). The 1-year cumulative pregnancy rate leading to term live birth rate was 43.4% in the mild group versus 44.7% in the standard group. The percentage of multiple pregnancies per ongoing pregnancy in 1 year of IVF treatment was 1.1% in the mild strategy and 29% in the standard strategy (p < 0.001, Chi-square test). The incidence of ovarian hyperstimulation syndrome requiring outpatient visits or hospital admission was 1.3% in the mild treatment group and 3.6% in the standard treatment group (p = 0.04, Chi-square test). For an extensive description of the characteristics and clinical outcomes see our earlier publication (220).

Table 2. Characteristics of 404 patients randomised to the mild strategy or the standard strategy of IVF

	Mild	Standard	P
Randomised (n)	205	199	
Mean number of cycles within 1 year (n)	2.3	1.7	P < 0.001
Pregnancy within 1 year leading to term live birth (n)	86	86	NS
Cumulative term live birth rate within 1 year (%)	43.4	44.7	NS
Multiple pregnancies per randomised couple (%)	0.5	13.1	P < 0.001

Source: Heijnen, 2006 (Heijnen et al., 2006)

Costs per cycle

The response rate of the economic evaluation questionnaires during treatment was 81% for all IVF cycles and did not differ significantly between the 2 treatment strategies. Almost 75% of the pregnant women responded to at least two of the three economic evaluation questionnaires during pregnancy and the neonatal period. The mean direct medical costs per IVF cycle were lower for the mild strategy (€1,569 versus €1,987; p=0.001), mainly due to lower costs for medication and technical procedures (Table 3). Per cycle, women in the mild treatment strategy had on average fewer days of sick leave during pregnancy as compared with the standard treatment strategy (23 versus 30; p=0.029).

For the mild strategy, the duration between cycles was shorter (88 ± 49 days versus 109 ± 38 days; p < 0.001). The cumulative treatment costs of the standard treatment strategy were higher in the first four months. However, over the complete 12 month period, treatment costs of the mild treatment strategy were comparable with those of the standard strategy (Figure 2).

IVF treatment, pregnancy, and the neonatal period revealed lower total costs for the mild strategy (€8,333 versus €10,745; p=0.006), represented in Table 4. The

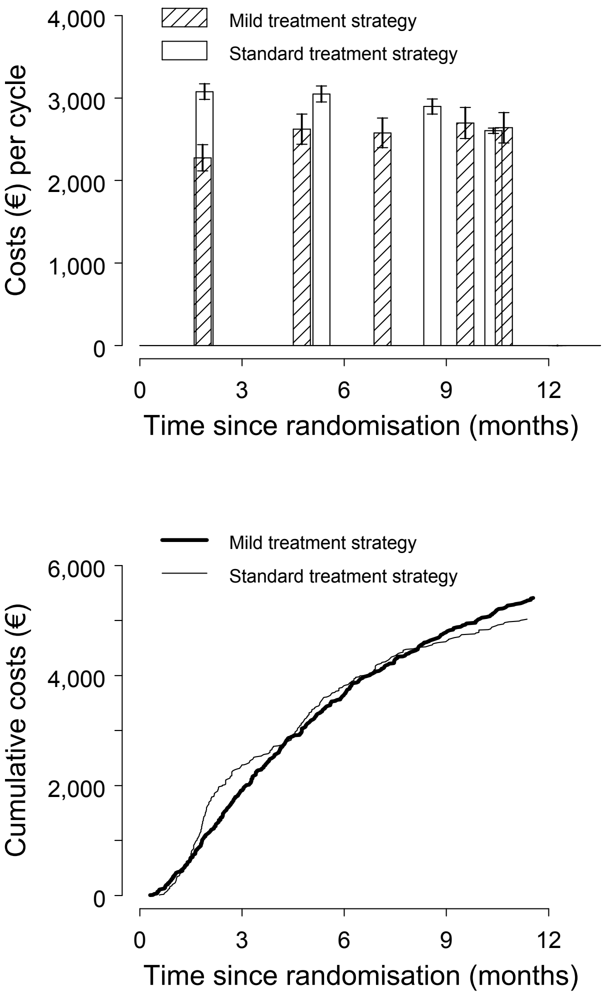

Figure 2. Mean treatment costs per cycle (bars) and cumulative treatment costs (lines) within 12 months after starting IVF in 404 couples, comparing the mild approach (hatched) with the standard approach (white). The median time since randomisation of each cycle is indicated by the placing of the bars.

costs of intramural care during IVF treatment was significantly higher for the mild strategy (€750 versus €576; p=0.006), which is due to the higher mean total number of cycles within one year. The medical costs during pregnancy for the mild strategy were half the costs of the standard strategy (€530 versus €1,061; p=0.03), due to the requirement for more medical care (outpatient visits, hospital admissions). Furthermore, the costs of the obstetric and postnatal period per ongoing pregnancy were significantly higher for the standard strategy, due to more hospital admissions and more prolonged duration in hospital for mother and child. The cost per ongoing pregnancy leading to term live birth was €19,156 in the mild strategy and €24,038 in the standard strategy.

Table 3. Intramural medical costs (€) per cycle for the standard and mild IVF treatment

	Mild			Standard			Significance[1]
	(Mean	±	SD)	(Mean	±	SD)	P
Medication							
GnRH analogue[2]	155	±	71	235	±	70	< 0,001
FSH	585	±	236	816	±	337	< 0,001
Technical procedures							
Oocyte retieval and laboratory	323	±	210	352	±	184	0,038
Embryo transfer	151	±	112	222	±	110	< 0,001
Embryo cryo transfer	17	±	68	14	±	60	NS
Intramural care							
Ultrasound	151	±	69	157	±	94	NS
Hospital admission	26	±	167	72	±	471	0,059
Control visits	42	±	51	43	±	59	NS
laboratory	108	±	123	65	±	82	< 0,001
Total costs per cyclus	1,559	±	608	1,977	±	803	0,001

[1]independent groups t-test

[2]GnRH antagonist for mild treatment and GnRH agonist for standard treatment

Table 4. Total costs (€) of IVF treatment in 404 patients within 12 months including costs of resulting pregnancy up to 6 weeks after delivery (per couple)

	Mild			Standard			Significance[1]
	(Mean	±	SD)	(Mean	±	SD)	P
IVF treatment							
Technical procedures	1,083	±	734	991	±	584	NS
Intramural care	750	±	561	576	±	693	0,006
Medication	1,626	±	1,088	1,737	±	1,069	NS
Indirect costs[2]	1,948	±	2,280	1,740	±	1,845	NS
Pregnancy and delivery							
Medical costs during pregnancy	530	±	984	1,061	±	2,076	0.03
Delivery	449	±	931	504	±	854	NS
Neonatal period							
Hospital admission mother	542	±	375	1,088	±	1,164	<0.001
Hospital admission child	342	±	374	1,653	±	1,337	<0.001
Maternity care	684	±	498	593	±	348	NS.
Indirect costs[2] *(pregnancy+neonatal)*	379	±	1,177	802	±	2,270	0,03
Total costs	**8,333**	±	**5,418**	**10,745**	±	**11,225**	**0,006**

[1] independent groups t-test

[2] indirect costs involve transportation costs and absence from work/sick leave

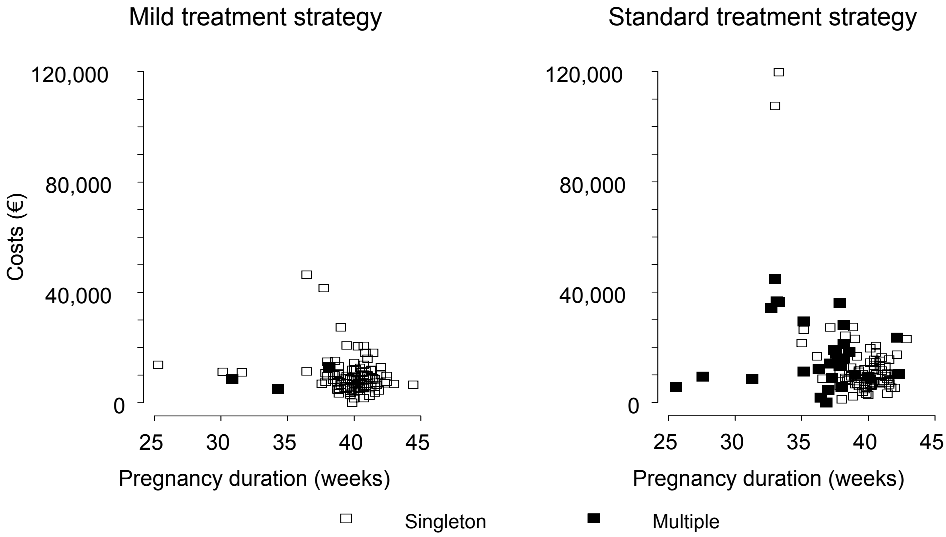

Figure 3. Total costs (€) of IVF treatment up to 6 weeks after calculated term, comparing singleton (open bullet) with multiple (black bullet) pregnancies by gestation duration.

Figure 3 illustrates the extent to which the higher costs for the standard strategy can be attributed to multiple pregnancies. Within 12 months after randomisation there were 16 pregnancies leading to preterm live birth (< 37 weeks) in the standard treatment group, versus 6 in the mild treatment group (p=0.02) as illustrated by Figure 3. Early pre-term life birth (< 32 weeks gestation) resulted in relatively low costs, primarily due to a relatively low neonatal survival rate. Late pre-term life birth (32-37 weeks gestation) did result in relatively high total IVF treatment costs.

Discussion

We have previously published the clinical data of this study, which showed that in women younger than 38 years, a mild strategy in IVF may result in similar ongoing pregnancy rates leading to cumulative term live births within 1 year compared with a standard strategy, while greatly reducing multiple pregnancy rates (220). In the current study we measured the consequences of both IVF treatment strategies in terms of costs in order to give an integrated evaluation of the health economics of the two treatment strategies. The overall costs during 12 months of treatment were lower for the mild strategy compared with the standard strategy, despite a higher average number of IVF cycles for the mild strategy. This is mainly due to the benefit of the reduction of multiple pregnancies and thereby reduction of pre-term life birth in the mild strategy.

The real advantage of the mild strategy is the avoidance of the very high long-term costs resulting from the increased morbidity of twins after birth (35,222,223). In the current study, the neonatal costs were covered until 6 weeks after expected date of delivery. The long-term medical prognosis for the children born in this study period cannot be predicted but the future costs for these children (in some cases severely ill) are likely to be very large (211). The incidence of disabilities is markedly increased in multiple pregnancies, and the associated long-term costs would certainly have impact on cost analysis because indirect long term costs will out way perinatal costs (222,211). This strengthen our conclusion that the mild treatment strategy with SET is much more cost-effective. Standard used effectiveness outcomes in economic evaluation studies, such as quality adjusted life-years were not employed, because their use in certain pregnancy situations can be difficult to interpret and sometimes misleading (224).

The findings of an earlier randomised controlled trial were consistent with the results of the present study, showing lower total costs with the SET strategy as compared with the dual embryo transfer (201,219). Moreover, the SET strategy also resulted in a marked reduction in the costs of paediatric health care, due to a considerable reduction of multiple pregnancies (201). Another randomised trial concluded that one cycle SET was less expensive, but also less effective compared to one cycle dual embryo transfer. It depends on the society's willingness to pay for one extra IVF cycle, whether a single cycle dual embryo transfer is preferred from a cost-effectiveness point of view (219). Other studies comparing costs of SET and dual embryo transfer were not randomised controlled trials, but all used theoretical extrapolations or decision-analytic calculations (35,54,55). De Sutter and colleagues suggested that the cost per child born was the same for single as for dual embryo transfer (35). This was explained by the fact that higher pre- and neonatal cost due to multiple pregnancies arising after dual embryo transfer balanced by higher cost for more SET cycles needed to obtain the same number of children (56). However, when costs are calculated per term live birth instead of child born (and a twin was calculated as one instead of two) costs for dual embryo transfer would be more expensive than for SET, which can be explained by the four fold higher cost of pregnancy of a twin instead of a singleton that they used in their calculations. When calculating the chance of term live birth per 12 months per couple, we counted twin live births as being equivalent to 1 live birth. It may be argued that a term-born twin should count as 2 live births. A term born twin may be perceived as a positive outcome, reducing the need for subsequent IVF treatments. However, in addition to the increased perinatal morbidity, mortality and long term health consequences associated with twin pregnancies, parents of multiple pregnancies have shown to be at greater risk of depression and anxiety (207,208). Furthermore, when weighing the benefits of the transfer of 1 or 2 embryos, account should also be taken of the live births which may occur following the subsequent transfer of surplus embryos (209), of which more will remain when just one fresh embryo is transferred.

In general, performing more mild IVF treatment strategies will increase the number of cycles needed to obtain the same number of live births when compared with the standard treatment strategy. Despite this higher average number of cycles for the mild strategy, and thereby high treatment costs, we found in our study that overall costs per term live birth were cheaper compared to the standard treatment strategy, mainly due to the health economic benefits of the reduction of multiple pregnancies in the mild stimulation approach. The impact of multiple gestations and their associated complications on costs is dramatic.

The debate is ongoing whether twins should be regarded as a success (6). From a clinical perspective, a term twin birth without complications may be reported as success. However, the increased rate of complicated deliveries, pre-term births, and low birth weight (all giving rise to increased chances for perinatal morbidity or mortality and long term health consequences) and negative psychosocial implications for parents or children (18) associated with twin pregnancies, have led to the opinion that medical intervention in infertility should preferably aim at establishing a singleton pregnancy (163,84). This study might contribute to the introduction of single embryo transfer on a large scale. The clinician and health care providers should be aware that an extra treatment cycle may be considered a low medical price for the prevention of the lifelong compromised quality of life. The couple should be made aware of the balance between their short-term desire for offspring and the long-term appreciation of healthy children. If structured, written information about risks and complications of multiple pregnancies and the consequences of the transfer of fewer embryos is provided, patients may become more inclined to the transfer of 1 embryo rather than 2 (57,116). An adequate reimbursement system is an important point to make single embryo transfer work (48). Society will carry a large part of the costs for the complications associated with multiple pregnancy and birth. Governments therefore might have regulatory interest in how IVF is performed. By funding IVF, they will accrue costs in the short term, but might also be able to establish guidelines for the number of embryos transferred. The possible need for higher number of treatment cycles, to achieve pregnancy after one-embryo transfer, might increase treatment costs. However, in the long run, governments will profit by saving the costs of complications associated with multiple pregnancies.