*Chapter* | *6*

# A mild strategy in IVF results in favourable outcomes in terms of term live birth, cost and patient discomfort

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*Submitted*

## Introduction

In vitro fertilization (IVF) is a complex treatment for infertility involving costly ovarian stimulation regimens (64), substantial patient discomfort (111,32) and considerable chances of complications (138,6). Applied ovarian stimulations protocols aim to generate many oocytes in order to compensate for inefficiencies in the laboratory procedures and to generate multiple embryos for transfer into the uterus.

Standard stimulation protocols involve the co-treatment with GnRH agonists to desensitize the pituitary gland (199). In contrast to GnRH agonists, GnRH antagonist treatment can be limited to the days in the mid-to late follicular phase at risk for a premature LH rise (58) allowing for the endogenous inter-cycle FSH rise to be utilized rather than suppressed (178). Mild stimulation protocols in which exogenous FSH administration is limited to the mid to late- follicular phase of the menstrual cycle have been shown to represent a feasible novel approach in stimulating growth of multiple dominant follicles for IVF (111,112). A potential drawback of GnRH antagonist co-treatment may be a minor reduction in efficacy per cycle (26). However, mild stimulation protocols may reduce patient discomfort by diminishing symptoms associated with pituitary down regulation (111) leading to fewer drop-outs from IVF (200), and thereby creating additional pregnancy chances in subsequent IVF cycles (32).

Significantly increased infant mortality and morbidity associated with premature birth have led to (higher order) multiple pregnancies being considered as the most important complication associated with IVF treatment (117). The financial impact of multiple births on health care resources has been shown to be greater than the costs of IVF treatment itself (201,173). Multiple pregnancies arising from IVF can be avoided by the transfer of a single embryo (SET). The observed minor decrease in pregnancy rate per cycle following SET can be overcome by establishing a high-quality cryopreservation program for surplus embryos (providing additional pregnancy chances after transfer in subsequent cycles) (173,43) or by an additional IVF cycle (41). An increasing number of Northern European centers currently offer SET as standard practice in a young women (202,203). However, the widespread implementation of SET into daily practice is hindered by the perceived need to maximize pregnancy chances per cycle (163).

Further development of IVF may be facilitated by challenging current concepts of "success" in assisted reproduction (105). Defining success in terms of chances for term live birth (or healthy child) per IVF treatment period (which may include multiple cycles) in relation to cost, patient discomfort and chances for complications as recently suggested by the Cochrane Menstrual Disorder and Subfertility group (204) would reduce the emphasis on maximizing single cycle outcome. Strategies involving shorter and milder ovarian stimulation protocols (including GnRH antagonist co treatment) and single embryo transfer may allow for more IVF cycles in the same period of time, resulting in similar term

live birth rate per treatment period despite a minor reduction in birth rate per treatment cycle. Moreover, such a mild strategy may reduce patient discomfort by using a milder stimulation protocol while lowering costs by virtually eliminating multiple pregnancies. The present multi-centre effectiveness study was designed to test the hypothesis that a mild in vitro fertilization strategy can achieve the same term live birth rate within 1 year compared to standard treatment, while reducing patient discomfort, multiple pregnancies and cost.

## Methods

### Patients

Patients with an indication for IVF or IVF/ Intracytoplasmic Sperm Injection (ICSI) based on tubal, male or unexplained infertility were recruited in two Academic Medical Centers (Rotterdam and Utrecht) between February 2002 and March 2004 (205). Patients under < 38 years with a 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.



### Study Design

This study was designed as a 2-arm randomised controlled, non-inferiority, effectiveness trial (205). The study was approved by the local ethics committee of both participating centers and all patients signed informed consent. Patients were randomly assigned to undergo either a mild ovarian stimulation with GnRH antagonist co-treatment combined with SET ("mild" treatment group) or a standard ovarian stimulation protocol including a GnRH agonist long-protocol combined with the transfer of 2 embryos ("standard" treatment group). In order to compensate for a possible reduction in pregnancy rate, patients in the mild treatment group were offered an extra reimbursed cycle on top of the three cycles normally reimbursed in the Netherlands. It was estimated that within 1 year after commencing treatment, the majority of subjects undergoing standard treatment would complete 3 cycles whereas those undergoing the shorter, mild treatment would complete 4 cycles.

The randomisation sequence was computer generated with random blocks of size 4 and 6, stratified by center in order to maintain balance between the two groups within both centres. The allocated treatment assignments were subsequently put in numbered sealed envelopes available at a central location in both centres. Envelopes were opened by the treating physician at the IVF-intake after written informed consent was obtained.

In the mild treatment group ovarian stimulation was performed by a fixed starting dose of 150 IU recombinant FSH (recFSH) (Gonal-F®; Serono Benelux B.V., Amsterdam, The

Netherlands, or Puregon®; N.V. Organon, Oss, The Netherlands) subcutaneous (s.c.) per day, initiated on cycle day 5. GnRH antagonist co-treatment 0.25 mg/day (Cetrorelix®; Serono Benelux B.V. or Ganirelix®; N.V. Organon) was administered if at least 1 follicle ≥ 14 mm diameter was observed by ultrasound, as previously described (112). The starting day or dose of recFSH could be adjusted in subsequent cycles. Induction of final oocyte maturation by human chorionic gonadotropin (hCG), oocyte retrieval, fertilization *in vitro* and luteal phase supplementation was performed according to standard procedures, as described previously (205). Only the best quality embryo was transferred (176) on day 3 or 4 of culture. Supranumerary high quality embryos were cryopreserved and thawed for transfer in a subsequent unstimulated cycle, as previously described (177). One or 2 embryos were transferred after cryopreservation according to patient preference. Cryopreserved embryos were thawed for transfer before continuing to a subsequent IVF cycle.

In the standard treatment arm, a GnRH agonist (leuproreline 0.2 mg/day, Lucrin®; Abbott B.V., Amstelveen, The Netherlands; or triptoreline 0.1 mg/day, Decapeptyl®; Ferring B.V., Hoofddorp, The Netherlands) was started in the midluteal phase of the preceding cycle. After approximately 2 weeks of GnRH agonist administration, ovarian stimulation was initiated with a starting dose of 150 IU/day recFSH s.c.. The recFSH dose could be adjusted in subsequent cycles, if considered necessary. Similar criteria were applied for hCG administration, for oocyte retrieval and fertilization procedures as in the mild treatment group. A maximum of 2 (best quality) embryos were transferred after culturing for 3 to 4 days. Standard luteal phase support, and criteria for cryopreservation of embryos were applied.

The primary outcome parameters chosen for this study were: (1) pregnancy within one year of treatment after randomisation leading to term (≥ 37 weeks gestation) live birth, (2) total costs per couple and child up to 6 weeks after expected delivery, and (3) patient discomfort and distress during IVF treatment.

### Cost calculations

The costs of the two IVF strategies were distinguished into two stages: costs of IVF treatment itself ending with the outcome of the last IVF-cycle (being pregnant, no pregnancy or drop out), and the costs of antenatal, peri- and post partum care until 6 weeks after the expected delivery date in women who had conceived within the treatment period.

The volumes of health care use were multiplied by the corresponding unit prices. The costs of IVF treatment were calculated from direct medical costs associated with care and indirect non-medical costs (travel and time costs, absence from work). The costs of pregnancy and obstetric care were distinguished into direct medical costs in the hospital (secondary obstetric care), direct medical costs outside the hospital (e.g. primary obstetric care, GP care, etc.) and indirect non-medical cost (206). Cost volumes were recorded

with case record forms (CRFs), hospital-based management and budgetary information systems, patient questionnaires and literature (205).

### Evaluation of patient stress and discomfort

The Hospital Anxiety and Depression Scale (HADS) (range: 0-21) (197), the somatic subscale of Hopkins Symptom Checklist (HSCL-S) (range: 0-24) (194) and the Subjective Sleep Quality Scale (SSQS) (range: 10-0) (196), were used to assess patient stress (anxiety and depression), physical discomfort and sleep quality, respectively. These questionnaires have been described elsewhere (205). Women completed the questionnaires at baseline (just after randomisation), directly following the first embryo transfer and one week after the outcome of subsequent cycles (cancellation, pregnancy test).

To estimate overall patient discomfort during the first year after randomisation, the 'area under the cumulative score within 12 months' curves were calculated per patient for the 4 psychological dimensions. These areas were compared between the study groups with ANCOVA, after adjusting for baselines scores. As more cycles were to be expected in the mild compared to the standard treatment group within 1 year (i.e. 4 instead of 3), this implies higher cumulative discomfort scores, given similar scores per cycle.



### Calculation of sample size

The total live birth rate after 3 cycles in the standard strategy was estimated at 45% with 30% twins. The expected costs per live birth were estimated at €26,000 using the total cost of one IVF treatment (€1,500) and cost of singleton and twin pregnancies (€5,300 versus €46,000) as described in the literature(109,55). It was expected that the mild strategy would result in a lower cumulative birth rate but also a lower twin pregnancy rate. A range of differences (from -5% to -15%) in live birth were tested and costs per extra live birth at each specified difference were calculated. At a difference of -12.5%, the cost per additional live birth in the standard strategy compared with the mild strategy was calculated to be 35,000 Euro. This was deemed to be excessive, and therefore -12,5% was used as the critical threshold for non-inferiority (205). Two hundred patients per arm were required to assure with 80% power that the lower bound of the 95% one-sided confidence interval around the difference in term live birth rate was within -12,5%.

### Statistical analysis

Statistical analysis was carried out according to the intention-to-treat principle. In addition, an analysis was performed in which switchers (patients who prefer another stimulation protocol or embryo transfer policy) were excluded. The Kaplan-Meier method was employed where patient drop-outs were considered to have a zero chance of a term live birth (no censoring) (107). In this way we established a statistical penalty for drop out due to unacceptable burden of the treatment. Patients who achieved an ongoing preg-

nancy *not* leading to term live birth were censored at the time that pregnancy occurred. The cumulative term singleton live birth was calculated using the same method. Couples who did not start a subsequent cycle within 6 months received a questionnaire in order to obtain all information about pregnancies occurring within 1 year after randomisation.

## Results

Four hundred and four patients were included in the study and a total of 769 cycles were performed within 1 year (444 in the mild group and 325 in the standard group). The flow-chart of the study according to CONSORT guidelines is shown in Figure 1.

The mean age in the total study population was 32.8 ± 3.1 (S.D.) years, the duration of infertility was 3.6 ± 2 years and the BMI was 23.1 ± 2.6 kg/m$^2$. The percentage of patients with primary infertility was 73.3%. The cause of infertility was 54.7% male factor, 16.6% tubal factor and 22.3% unexplained or other reason. Both treatment groups were comparable with respect to these patient characteristics (data not shown).

In the mild strategy group, 193 first, 136 second, 78 third, 31 fourth and 6 fifth IVF cycles were carried out within 1 year. In the standard group 186 first, 98 second, 35 third and 6 fourth IVF cycles were conducted. The mean number of started cycles, oocyte retrievals and embryo transfers in 1 year were respectively 2.3 ± 1.2, 1.8 ± 1.1 and 1.5 ± 1.0 in the mild group and 1.7 ± 1.0, 1.6 ± 0.9 and 1.4 ± 0.9 in the standard group (P-value respectively < 0.001; 0.008 and 0.5, t-test). The mean duration of injections was 8.5 ± 2.7 in the mild group and 25.3 ± 6.8 in the standard group (p<0.001),

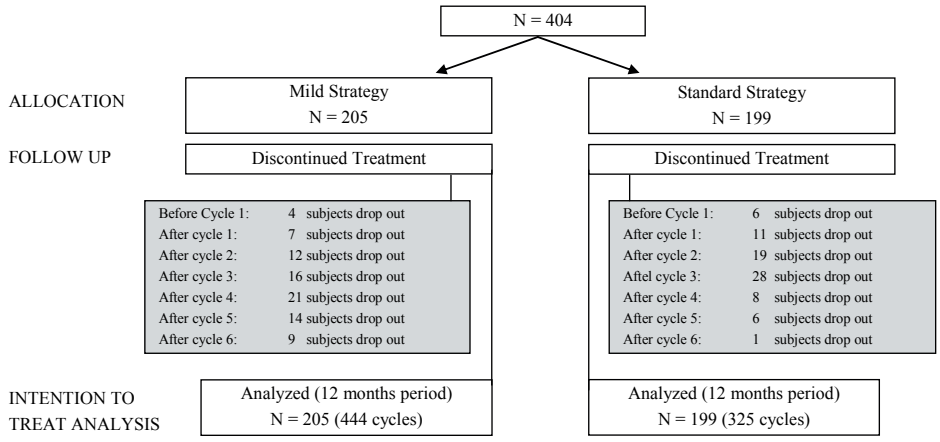


**Figure 1.** Flow chart according to the CONSORT guidelines showing the number of cycles analysed in the 12 months intention to treat analysis and the number of drop outs during the entire treatment.

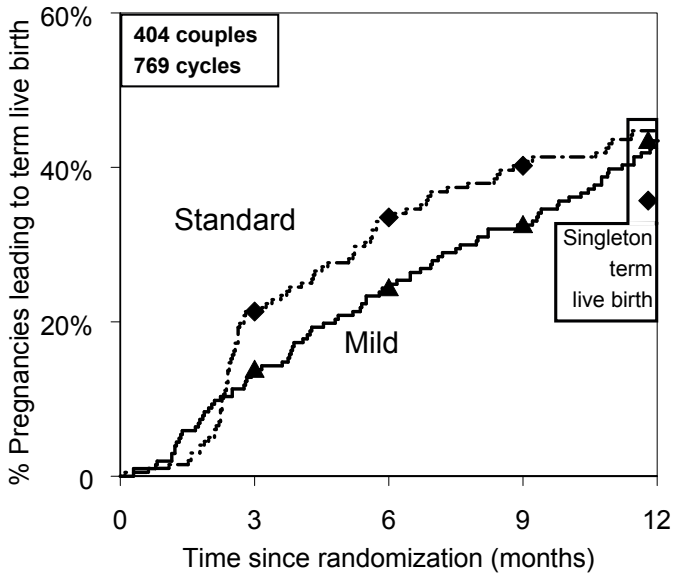


**Figure** 2. Realistic cumulative term live birth rate within 12 months after starting IVF in 404 couples, comparing a mild ovarian stimulation plus single embryo transfer strategy (triangles) with a standard ovarian stimulation plus dual embryo transfer strategy (diamonds). The singleton live birth rate after 12 months is also presented in the graph.



Out of 96 ongoing pregnancies in the mild treatment group within 1 year, 11 were spontaneous, 78 arose from fresh embryo transfer, 6 were from cryopreserved embryos and 1 occurred after 'escape' intra-uterine insemination due to low ovarian response to stimulation. The number of total term live births resulting from 1 year of mild treatment was 86. Out of 103 of ongoing pregnancies in the standard treatment group, 5 were spontaneous, 93 after fresh embryo transfer and 5 were from cryopreserved embryos. The number of total term live births resulting from 1 year of treatment was 86.

The 1-year cumulative rate of pregnancy leading to term live birth was 43.4% in the mild group and 44.7% in the standard group (Figure 2). The difference between the mild and standard group was 1.3% in favour of the standard group, with a lower limit of the one-sided 95% confidence interval equal to –9.8%. The percentage of multiple pregnancies per randomised couple in 1 year of IVF treatment was 0.5% (95% CI 0.0;2.7) in the mild strategy and 13.1% (95% CI 8.7;18.6) in the standard strategy ($P < 0.001$, Chi-square test). Table 1 shows the characteristics of children born from pregnancies within 12 months after starting IVF. The miscarriage rate was 15.0% in the mild group and 17.1% in the standard group. The 1-year cumulative rate of pregnancy leading to singleton term live birth after 1 year was 43.4% in the mild group and 35.7% in the standard group (Figure 2).

**Table 1.** Pregnancy outcome following IVF treatment (for a maximum of 1 year) comparing a mild versus standard strategy involving a total of 404 couples and 769 cycles.

| | **Mild Strategy*** | **Standard Strategy** | |
|---|---|---|---|
| | Singleton | Singleton | Multiple |
| Live Birth (total) (n) | 91 | 76 | 26 |
| Live born children (n) | 91 | 76 | 51** |
| Late preterm live birth (n) (≥ 32 - 37 weeks gestation) | 2 | 6 | 6 |
| Early preterm live birth (n) (< 32 weeks gestation) | 3 | 1 | 3 |
| Birth weight (g) | 3,339 ± 757 | 3,349 ± 757 | 2,340 ± 726 |

*One triplet occurred in the mild treatment group (Gestational age < 32 weeks, birth weight: 1340 gram).

**One twin pregnancy resulted in one intra-uterine death and one live birth

The difference in distribution of gestational age of the live births between the standard and mild treatment group is significant (p-value = 0.04).

In the mild treatment group 12 patients (5.8%) switched to another stimulation protocol or embryo transfer strategy, whereas 15 patients (7.5%) switched in the standard group. When excluding these patients in the analysis, the 1-year cumulative rate of pregnancy leading to term live birth rate was 43.2% in the mild group and 44.6% in the standard group.

The mild stimulation strategy resulted in lower average total costs per IVF treatment within 12 months and pregnancy up to 6 weeks after expected date of delivery (per couple and child) (€8,333 versus €10,745; P = 0.006, t-test*)* (Table 2). The IVF treatment costs within this period were similar for both strategies (€3,459 versus €3,304). The costs of the obstetric and postnatal period were higher for the standard strategy (€2,547 versus €4,899), due to more outpatient visits and hospital admissions, higher delivery costs, and greater absence from work, mainly caused by multiple pregnancies. The non-medical costs were also higher for the standard strategy (€2,327 versus €2,542).

**Table 2.** Total costs (€) of IVF treatment over 12 months including costs of pregnancies up to 6 weeks after delivery (per couple).

| | **Mild** | | **Standard** | | **Significance*** |
|---|---|---|---|---|---|
| | (Mean | ± SD) | (Mean | ± SD) | P |
| IVF Treatment | | | | | |
| *Technical Procedures* | 1,083 | ± 734 | 991 | ± 584 | *0.16* |
| *Medication* | 1,626 | ± 1088 | 1,737 | ± 1069 | *0.3* |
| *Monitoring* | 750 | ± 561 | 576 | ± 693 | *0.006* |
| *Indirect costs* | 1,948 | ± 2280 | 1,740 | ± 1845 | *0.3* |
| Pregnancy and neonatal period | | | | | |
| *Medical costs* | 2,547 | ± 4,553 | 4,899 | ± 10,746 | *0.01* |
| *Indirect costs* | 379 | ± 1,177 | 802 | ± 2,270 | *0.03* |
| **Total costs** | **8,333** | **± 5,418** | **10,745** | **± 11,225** | ***0.006*** |

* independent groups t-test

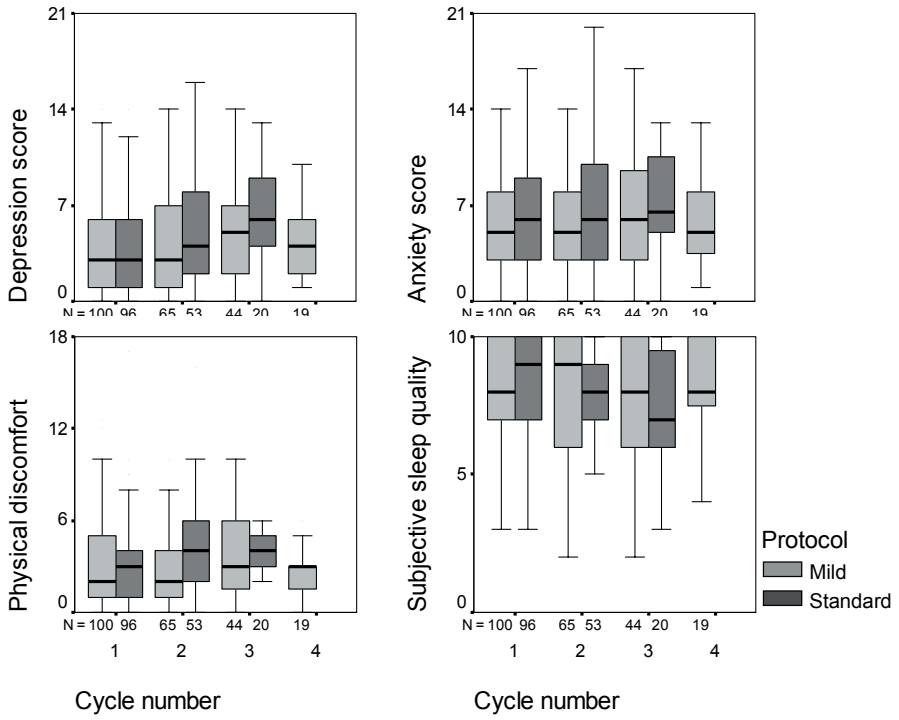




**Figure 3.** Adjusted means of the scores on the 4 psychological dimensions: Anxiety, Depression, Physical discomfort (higher score means more anxiety, depression and physical discomfort) and Subjective sleep quality (higher score means better sleep quality) of cycles performed for both the mild and the standard treatment group within 12 months.

Figure 3 shows the distribution of the raw scores for 4 psychological parameters in cycles performed during the first year after randomisation for both the mild and the standard group. The areas under the cumulative score curves over cycles performed within 12 months were equal among the two treatment strategies for scores on the HADS-A ($p = 0.9$), the HADS-D ($p = 0.8$), the HSCL-S ($p = 0.5$) and the SSQS ($p = 0.3$).

## Discussion

To our knowledge, the current study is the first randomised controlled trial comparing cumulative term live births, total costs per couple and patient stress after different treatment strategies during a given period of time rather than per treatment cycle. This study demonstrates that in women less than 38 years of age, a mild strategy in IVF involving GnRH antagonist co-treatment together with single embryo transfer results in similar 1-year cumulative pregnancy rates leading to term live birth compared with a standard

strategy. Moreover, overall patient discomfort within 1 year is similar despite a minor increase in average number of IVF cycles. Multiple pregnancy rates are greatly reduced and overall costs per term live birth are lower in the mild strategy group.

Previous studies focusing on outcomes in single cycles (40,157,43) have shown that SET in women less than 36 years is highly effective in reducing multiple pregnancies, but at the expense of a lower pregnancy rate per cycle. Although a reduced pregnancy chance per cycle was also observed for the mild strategy in the present study, similar cumulative 1-year pregnancy rates leading to term live birth of approximately 45% were shown to occur. In order to achieve this goal, the lower pregnancy rate per cycle is compensated by a slight increase in the average number of cycles. Because the duration of a mild stimulation cycle is shorter, more cycles can be performed in the same period of time. Therefore the percentage of couples finishing treatment within 1 year does not differ between the two groups (66.8% in mild group versus 71.9% in standard group ($p=0.3$)). When only singleton live birth was taken as a measure for treatment success, as proposed by some investigators (84), the 1 year cumulative term singleton rate was higher in the mild treatment group compared with the standard treatment group.

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. However, it may be argued that a term-born twin should count as 2 live births. Term-born twins 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 one compared with two embryos, account should also be taken of the live births which may occur following the subsequent transfer of surplus embryos (209).

Another methodological issue relevant to the present study is the means of calculating the cumulative pregnancy rates leading to term live birth. In this study, the Kaplan Meier method to calculate the 1-year cumulative pregnancy rates differs from the standard method often used in calculating cumulative success rates in infertility (107). Generally it is assumed that drop outs have a similar chance for pregnancy than patients continuing treatment (censoring). Because all information concerning pregnancies occurring in 1 year was available, an intention to treat analysis including all pregnancies could be performed to calculate the true cumulative term live birth rate without making assumptions with regard to the pregnancy chance among the drop outs (no censoring). Therefore, this cumulative term live birth rate is lower than usually found in the literature. Censoring does not punish for high drop out rates during treatment (for example due to patient discomfort) and is therefore not appropriate when outcome parameters are employed which take treatment-related stress into account.

Although more cycles were performed in the mild treatment group within one year,

overall patient discomfort was similar among the two strategies during that year. In calculating the cumulative discomfort score over time, the assessments of discomfort at the end of each IVF cycle were used. The stress level may have varied during and between treatment cycles. Nevertheless, patient discomfort associated with the mild strategy appeared to be stable over time whereas the level of discomfort related to standard treatment increased during subsequent treatment cycles. Questionnaires were returned by just 50% in both treatment groups. Although this may reflect the complexity and frequency of the measurements, the response rate was within normally reported ranges for this type of psychological assessment (210). The degree of non-response might have resulted in an underestimate of symptoms in both groups, since questionnaires were perhaps less likely to be completed by women under greater stress due to their perceived additional burden.

The potential health economic benefits arising from SET have thus far been the subject of few studies (35,54,55). A recently published randomised trial demonstrated a SET strategy to be associated with lower total costs per cycle compared to cycles were 2 embryos were transferred due to a considerable reduction of multiple pregnancies (201). Despite the higher average number of cycles performed with the mild strategy (and consequently higher monitoring and indirect costs) the overall costs per pregnancy within 1 year leading to term live birth were lower compared to the standard treatment strategy. This was mainly due to the reduction in multiple pregnancies. The postnatal period of cost assessment was limited to 6 weeks after the expected date of delivery. This probably resulted in a conservative estimate of the additional costs arising from premature deliveries, since prematurity often has in long term health consequences (211).



The findings of the current study highlight the medical, health economic and psychological benefits of mild strategies in women less than 38 years of age in IVF treatment. However, if these results are to be widely implemented, IVF outcomes should be redefined in broader terms, better reflecting the interests of the couple, the child and providers of health care. In other medical fields, such oncology, it is normal practice to present success of a treatment strategy as survival rate per given time period and also include side effects (212,213). The aim when embarking on IVF treatment is the delivery of a healthy baby (or babies) within a certain time period (consisting of a series of IVF cycles and subsequent replacement of frozen embryos). This needs to be weighed against the associated discomfort, chances for complications and costs. Adopting the endpoint 'term-delivery per time period' would encourage the adoption of patient friendly stimulation protocols and single embryo transfer. In conclusion, the findings of this study may contribute to the more widespread use of mild ovarian stimulation and SET in clinical practice. Additional measures required to aid widespread adoption of this approach will include better education of both patients and health care providers regarding the chance and definition of success, the risks associated with multiple pregnancies (48) and ideally, the institution of reimbursement systems which encourage, rather penalize SET (214,215).