A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial

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Summary

Background **Mild in vitro fertilisation (IVF) treatment might lessen both patients' discomfort and multiple births, with their associated risks.**[A: okay?] **We aimed to test the hypothesis that mild IVF treatment can achieve the same chance of a pregnancy resulting in term livebirth within 1 year compared with standard treatment, and can also reduce patients' discomfort, multiple pregnancies, and costs.**

Methods **We did a randomised, non-inferiority effectiveness trial. 404 patients were randomly assigned to undergo either mild treatment (mild ovarian stimulation with gonadotropin-releasing hormone [GnRH] antagonist co-treatment combined with single embryo transfer) or a standard treatment (stimulation with a GnRH agonist long-protocol and transfer of two embryos). Primary endpoints were cumulative pregnancy and term livebirth within 1 year after randomisation (with a non-inferiority threshold of –12·5%), total costs per couple up to 6 weeks after expected delivery, and overall discomfort for patients. Analysis was by intention to treat. This trial is registered as an International Standard Randomised Clinical Trial, number ISRCTN35766970.**

Findings **The proportions of cumulative pregnancies that resulted in term livebirth after 1 year were 43·4% with mild treatment and 44·7% with standard treatment.**[A: Please can you give absolute patient numbers for these proportions?] **The lower limit of the one-sided 95% CI was –9·8%. The proportion of couples with multiple pregnancy outcomes was 0·5% with mild IVF treatment versus 13·1% (p<0·001) with standard treatment, and mean total costs were €8333 and €10745, respectively (difference €2412, 95% CI 703–4131). There were no significant differences between the groups in the anxiety, depression, physical discomfort, or sleep quality of the mother.**[A: okay? or did you mean both parents?]

Interpretation **Over 1 year of treatment, cumulative rates of term livebirths and patients' discomfort are much the same for mild ovarian stimulation with single embryos transferred and for standard stimulation with two embryos transferred. However, a mild IVF treatment protocol can substantially reduce multiple pregnancy rates and overall costs.**

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Introduction

In-vitro fertilisation (IVF) is a complex treatment for infertility that entails costly regimens for ovarian stimulation,[1] serious discomfort to patients,[2] and substantial risks of complications.[3,4] Ovarian stimulation protocols aim to generate many oocytes to compensate for inefficiencies in laboratory procedures and to generate several embryos for transfer into the uterus. Conventional ovarian stimulation protocols include cotreatment with gonadotropin-releasing hormone (GnRH) agonists, to desensitise the pituitary gland.[5] By contrast, GnRH antagonists can be administered on only those days in the mid-to-late follicular phase of the menstrual cycle during which there is a risk of a premature rise in luteinising hormone (LH). This method allows the endogenous intercycle rise in follicle-stimulating hormone (FSH) to be utilised rather than suppressed.[6] Mild stimulation protocols, in which exogenous FSH is given only in the mid-to-late follicular phase, have been shown to be feasible for stimulation of growth of several dominant follicles for IVF.[2,7] Although reduction in effectiveness per cycle is a potential drawback of cotreatment with GnRH antagonists,[8,9] mild stimulation protocols could also lessen patients' discomfort by diminishing symptoms associated with pituitary down-regulation.[2] The resultant reduction in drop-outs could create additional pregnancy chances in subsequent IVF cycles.[10]

Because (higher-order) multiple pregnancies are associated with increases in infant mortality and morbidity, they are seen as the most important complication of IVF treatment.[4] The financial effect of multiple births on health-care resources has been shown to be greater than the cost of IVF treatment itself.[11,12] Multiple pregnancies due to IVF treatment can be avoided by transfer of a single embryo.[13] The reported decrease in the chance of pregnancy per cycle after single embryo transfer could possibly be overcome by establishment of a high-quality cryopreservation programme for surplus embryos (which would provide additional pregnancy chances in subsequent cycles),[14] or by additional IVF cycles.[15] A growing number of northern European centres offer single embryo transfer as standard practice for young women.[16] However, widespread implementation of single embryo transfer is hindered by a perceived need to ensure the maximum chance of pregnancy per cycle.[17]

[A: This paragraph has been moved to your discussion.]

Strategies with shorter ovarian stimulation protocols (such as GnRH antagonist cotreatment) and transfer of a single embryo could allow more IVF cycles in the same period as conventional treatment, and produce a similar proportion of term livebirths, despite a minor reduction in the proportion of term livebirths per treatment cycle. Moreover, mild strategies could reduce patients' discomfort and diminish costs associated with multiple pregnancies. We aimed to test this hypothesis—ie that a mild IVF protocol could produce a similar proportion of term livebirths to conventional treatment in the same period, and also reduce patients' discomfort, multiple pregnancies, and total costs per couple.[18] **[A: okay?]**

Methods

Participants and study design

We recruited patients with an indication for IVF or for a combination of IVF and intracytoplasmic sperm injection on the basis of tubal, male, or unexplained infertility at two academic medical centres in Rotterdam and Utrecht between February, 2002, and March, 2004.[18] Eligible patients had had no previous IVF treatment or had borne a healthy child after previous IVF treatment, were aged younger than 38 years, and had a menstrual cycle length of 25–35 days and a body-mass index of 18–28 kg/m^2.[18]

This study was designed as a parallel-group randomised, open-label, non-inferiority effectiveness trial.[18] The study protocol was approved by the local ethics review committee of the Erasmus Medical Centre, Rotterdam, and the University Medical Centre, Utrecht. Written informed consent was obtained from all patients before they were randomly assigned to mild or standard treatment groups.**[A: This information has been moved to the following section.]** To compensate for a possible reduction in probability of pregnancy per IVF cycle, patients were offered reimbursement for the costs of one extra cycle in addition to the three cycles normally reimbursed in the Netherlands. We estimated that within 1 year of the start of treatment, most patients undergoing standard treatment could complete up to three cycles, whereas those undergoing the shorter mild treatment could complete up to four cycles.[18]

Procedures and assessment

The randomisation sequence was computer generated; random blocks of size four and six were stratified by centre to maintain balance between the two treatment groups within each centre. The resultant sets of treatment assignments were put into numbered sealed envelopes and made available at each centre; envelopes were sequentially allocated to consecutive patients and opened by treating physicians at IVF planning consultations.

One treatment group was given mild ovarian stimulation, consisting of GnRH antagonist cotreatment, combined with single embryo transfer, and the other was given standard ovarian stimulation with the GnRH agonist long-protocol, combined with transfer of two embryos.[18] **[A: okay?]** Supernumerary high-quality embryos were cryopreserved and thawed for transfer in a subsequent unstimulated cycle before the start of a new IVF treatment cycle. These frozen-thawed embryo-transfer cycles were treated as a part of the previous IVF cycle. In both groups either one or two cryopreserved embryos were transferred, according to the patient's preference. Intervals between IVF cycles were determined by logistic reasons and patients' preference. Patients were treated by independent physicians.

The costs of the two IVF strategies for the financial year 2004 were divided into two stages: treatment itself, up to the outcome of the last IVF cycle, and antenatal, peripartum, and postpartum care until 6 weeks after the expected delivery date in women who conceived within the treatment period.[18] Costs of miscarriages and ectopic pregnancies were also taken into account. Data on resource use were collected for each individual from case-record forms and questionnaires. Real medical costs were calculated from a societal perspective, by use of the microcosting method.[19]

The hospital anxiety and depression scale (range 0–21), the somatic subscale of Hopkins symptom checklist (range 0–24), and the subjective sleep-quality scale (range 10–0), were used to assess patients' stress (anxiety and depression), physical discomfort, and sleep quality, respectively.[18] Women completed these questionnaires at baseline (just after randomisation), directly after the first embryo transfer, and 1 week after the outcomes of subsequent cycles (such as cancellations or pregnancy tests).[18] For assessment of patients' discomfort, the areas under the cumulative score within 12 months were compared between study groups by use of ANCOVA, after adjustment for baseline scores.

Primary outcome measures were pregnancy and term livebirth within 1 year of randomisation; total costs per couple and child up to 6 weeks after expected delivery; and patients' discomfort.[18]

Statistical analysis

200 patients per group were needed to assure with 80% power that the lower limit of the 95% one-sided CI for the difference in the proportion of term livebirths was within a prespecified non-inferiority boundary of 12·5%.[18] **[A: Why is no upper confidence interval reported? If the upper bound cannot be calculated due to negative ICER values, this should be stated.]** The standard treatment strategy was assumed to have a 45% cumulative chance of success.[18] Data were analysed according to the principle of intention to treat. All pregnancies within 1 year of randomisation were analysed, whether achieved by IVF, cryopreservation, intrauterine insemination, or spontaneous conception. To ensure that the comparison of treatment strategies was not affected by patients who changed to a different stimulation protocol or embryo-

transfer policy, another analysis was done without these patients. The Kaplan-Meier method was used to calculate the 1-year cumulative proportion of term livebirths; patients who withdrew from IVF treatment were not censored.**[A: okay?]** Spontaneous pregnancies after patients withdrew from treatment were included in analysis. Patients who achieved a continuing pregnancy that did not lead to term livebirth were censored when they became pregnant. Cumulative term singleton livebirths were calculated by the same method.

To show that 1 year was sufficient for most patients to finish treatment, we calculated the proportion of term livebirths after four IVF cycles with mild treatment and three cycles with standard treatment. Couples who did not start a subsequent cycle within 6 months received a questionnaire to obtain all information about pregnancies that happened within 1 year after randomisation. We analysed all cycles finished before 1 year after randomisation—whether cancelled, pregnant, or non-pregnant.

We calculated costs for each cycle and also total costs per patient, accumulated over 1 year. Patients who withdrew before 1 year were assumed to have incurred no further costs related to treatment. Difference in mean total costs between the two treatments was calculated with a two-sample *t* test.[18] The difference in cumulative percentages was used to represent the difference in mean cost-effects (since pregnancy is a binary outcome).**[A: One reviewer requested that you include a sentence explaining this point – is this okay?]** This trial is registered as an International Standard Randomised Clinical Trial, number ISRCTN74651862.

Role of the funding source

This study was funded by ZonMw (Netherlands), programme Doelmatigheidsonderzoek. This funding source had no role in study design, data collection, analysis, interpretation, or writing of the report. The first author had full access to all data and final responsibility for the decision to submit the paper for publication.

Results

404 patients were included in the study, and randomly assigned to either mild or standard treatment groups (figure 1). The mild and standard groups did not differ from each other in terms of baseline clinical and demographic characteristics (table 1). We did 769 IVF cycles in 1 year (444 in the 205 patients treated with a mild IVF strategy and 325 in the 199 patients treated with standard protocols).**[A: Data on numbers of cycles have been included in figure 1.]** For mild treatment, the mean number of started cycles was 2·3 (SD 1·2); the mean for oocyte retrievals was 1·8 (1·1); and a mean of 1·5 (1·0) embryo transfers were done in 1 year. **[A: Please confirm that these are standard deviations.]** For standard treatment, these means were 1·7 (1·0), 1·6 (0·9), and 1·4 (0·9), respectively (p <0·001, 0·008, and 0·5, respectively,

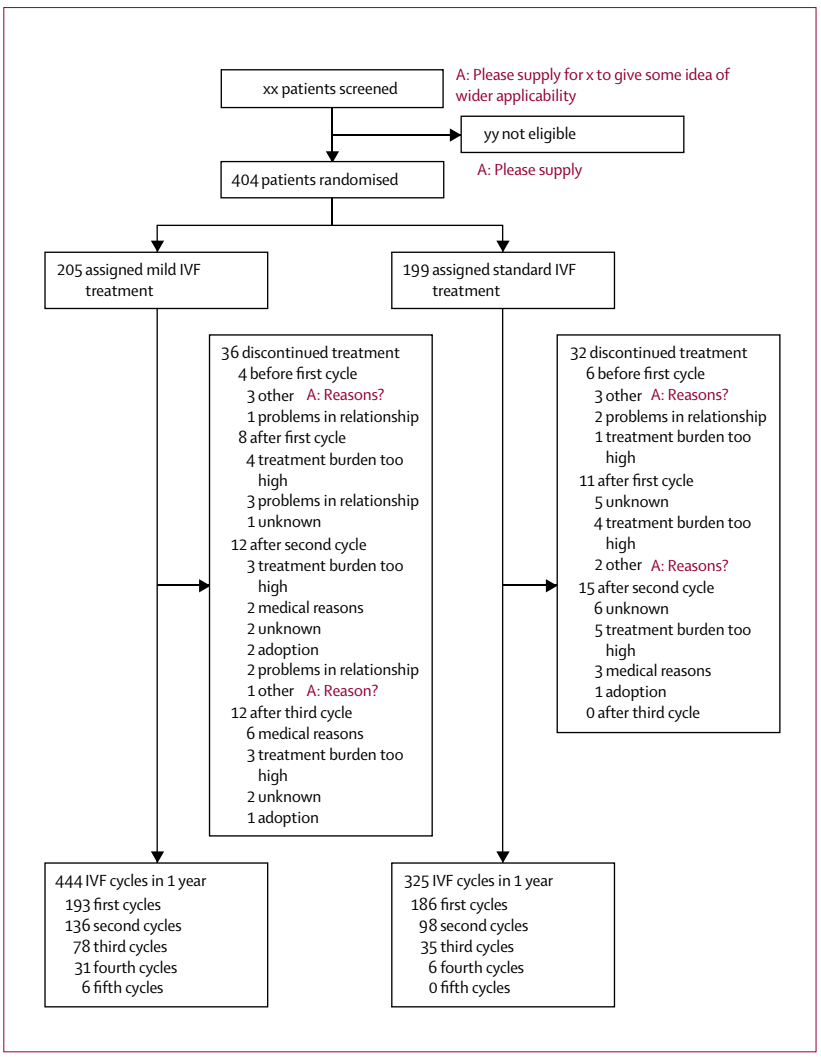

Figure 1: **Trial profile**
Reason for withdrawals do not include pregnancy or preference for another stimulation protocol or embryo transfer policy.

	Mild (n=205)	Standard (n=199)
Age of women (years)	32·9 (3·1)	32·8 (3·2)
Body-mass index (kg/m²)	23·0 (2·6)	23·2 (2·5)
Duration of infertility (years)	3·6 (1·9)	3·6 (2·1)
Primary infertility	73·7%	72·9%
Child after previous IVF treatment	6·4%	5·6%
Cause of infertility		
Male	108 (53%)	113 (57%)
Tubal	31 (15%)	36 (18%)
Unexplained	55 (27%)	36 (18%)
Other	11 (5%)	15 (8%)

Values are mean (SD) or number (%) of patients.

Table 1: **Baseline demographics and clinical characteristics of patients assigned to mild or standard treatment**

	Mild treatment (n=444)	Standard treatment (n=325)	p
Duration of ovarian stimulation (days)	8·3 (2·2)	11·5 (3)	<0·001*
Duration of injections (days)	8·5 (2·7)	25·3 (6·8)	<0·001*
Total dose of follicle stimulating hormone (IU)	1307 (529)	1832 (758)	<0·001*
Cancellation of pregnancy cycle	80 (18·0%)	xx (8·3%)	<0·001†
Number of oocytes per retrieval	6·9 (4·8)	8·5 (4·3)	<0·001*
‡Number of embryos per retrieval	2·8 (2·7)	3·8 (2·9)	<0·001*
Number of cryopreserved embryos *vs* fresh embryos for transfer **[A: okay?]**	0·9 (1·8)	0·6 (1·4)	0·04*
Continuing pregnancy per started cycle (fresh embryos)	78 (17·6%)	93 (28·6%)	<0·001†
Continuing pregnancy per started cycle (cryopreserved embryos)	6 (1·4%)	4 (1·2%)	0·8†
Term livebirth per started cycle (fresh embryos)	70 (15·8%)	78 (24·0%)	0·003†
Term livebirth per started cycle (cryopreserved embryos)	49 (1·1%)	3 (0·9%)	0·8†
§Ovarian hyperstimulation syndrome	6 (1·4%)	12 (3·7%)	0·04†

Values are mean (SD) or number (%) of cycles. **t* test for difference or †Pearson χ^2 test for difference. **[A: Please give actual p values unless smaller than 0.0001.]** ‡Embryos suitable for embryo transfer. §Mild, moderate, and severe ovarian hyperstimulation syndrome. **[A: Please provide number for xx]**

Table 2: **Cycle-specific characteristics of IVF cycles finished within 1 year**

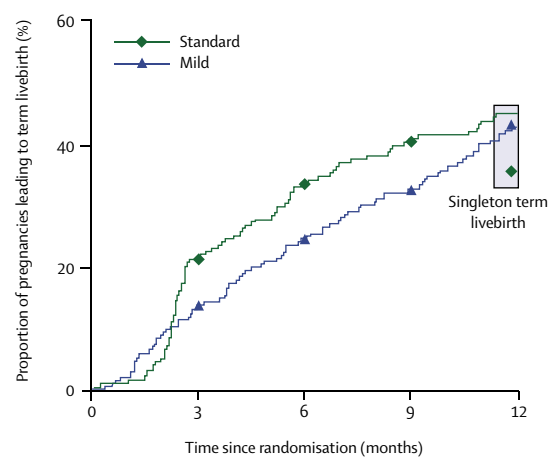

Figure 2: **Cumulative term livebirth rate within 12 months after starting IVF**
[A: In a Kaplan-Meier plot we need to provide the number of patients who still have a chance of pregnancy at each stage.]
Mild: mild ovarian stimulation with GnRH and single embryo transfer
Standard: standard ovarian stimulation with GnRH and dual embryo transfer.
The shaded area represents the singleton livebirth rate after 12 months.**[A: okay? Please check this is correct]**

by use of the t-test).**[A: Please give actual p value, unless it is smaller than 0.0001]** Table 2 shows cycle-specific characteristics of the IVF cycles finished within 1 year.

Of 96 continuing pregnancies (positive heartbeat on ultrasonography 10 weeks after embryo transfer) in the mild treatment group during the year-long study, 11 were spontaneous, 78 arose from fresh embryo transfer, six were from cryopreserved embryos, and one took place after so-called escape intrauterine insemination due to low ovarian response to stimulation. Of 102 continuing pregnancies in the standard treatment group, four were spontaneous, 93 happened after fresh embryo transfer, and five were from cryopreserved embryos. 86 term livebirths were produced in each of the two groups after 1 year of treatment.**[A: okay?]**

Figure 2 compares the 1-year cumulative proportion of pregnancies that produced term livebirths—43·4% with mild IVF treatment and 44·7% with the standard protocol. Standard IVF treatment resulted in 1·3% more term livebirths than mild treatment; the lower limit of the one-sided 95% confidence interval was –9·8%. The proportion of multiple pregnancies per couple during 1 year of IVF treatment was 0·5% (95% CI 0–2·7) with the mild strategy and 13·1% (8·7–18·6) with the standard strategy ($p<0·001$, χ^2 test).[**A: Please give actual p value, unless it is smaller than 0.0001]** Table 3 shows the characteristics of children born from pregnancies within 12 months after randomisation. The proportion of miscarriages was 15·0% with mild treatment and 17·1% with standard treatment. Figure 2 shows that the cumulative proportion of pregnancies leading to singleton term livebirth after 1 year was 43·4% in the mild group and 35·7% in the standard group.

36 and 32 patients withdrew from mild and standard treatment, respectively, for reasons shown in figure 1. Although these patients withdrew at various stages during treatment, the study design allowed comparison of drop-out rates only for the first two treatment cycles. The drop-out rate for mild treatment was 5·1% after the first cycle and 11·2% after the second, compared with 9·1% and 19·5%, respectively, for standard treatment. The drop-out rate per cycle was significantly lower in the mild treatment group than in the standard group (odds ratio = 0·53, 95% CI 0·28–0·98, p=0·04, corrected for cycle number). Patients who withdrew were significantly younger than those who finished treatment, with a mean age of 32·3 years (SD 3·4) and 33·3 years (3·2),

	Mild strategy		Standard strategy	
	Singleton	Multiple*	Singleton	Multiple
Livebirths (total)	91	1	76	26
Liveborn children	91	3	76	51†
Term livebirth (≥37 weeks' gestation)	86	0	69	17
Late preterm livebirth (32–37 weeks' gestation) **[A: okay?]**	2	0	6	6
Early preterm livebirth (<32 weeks' gestation)	3	1	1	3
Birthweight (kg)‡	3·34 (0·76)	1·34	3·35 (0·76)	2·34 (0·73)

*One set of triplets were born in the mild treatment group after intrauterine insemination in a cycle that was cancelled because of monofollicular growth. †One twin pregnancy resulted in one intrauterine death and one livebirth. ‡Birthweight is mean (SD). For multiple pregnancies the mean birthweight of the twins or triplets was used to calculate the overall mean birthweight per treatment group. The difference in distribution of term, late preterm, and early preterm livebirths between the standard and mild treatment group is significant (p=0·04, χ^2 test with continuity correction).

Table 3: **Pregnancy outcome after mild and standard IVF treatment**

respectively (p=0·047). However, those who withdrew did not have significantly different durations of infertility (p=0·4) or pregnancy histories (p=0·7). Cycle cancellation or the number of oocytes retrieved did not significantly affect drop-out rates (p=0·4 and p=0·6 respectively, corrected for cycle number). 12 patients (6%) given mild treatment and 15 (8%) given standard treatment switched to another stimulation protocol or embryo-transfer strategy. When these patients were excluded from analysis, the 1-year cumulative proportion of pregnancies leading to term livebirth was 43·2% in the mild group and 44·6% in the standard group.

The proportion of pregnancies leading to a term livebirth was 50·3% after the completion of three standard cycles and 52·4% after completion of four mild cycles. The difference, of 2·1% in favour of the mild strategy, has a lower one-sided 95% confidence bound of –6·6%.

Table 4 shows the lower total costs associated with mild treatment (difference €2412, 95% CI 703–4131). Therefore, the incremental costs per additional pregnancy leading to term livebirth with standard treatment group, compared with mild treatment, would be €185 000 (€2412/(0·447–0·434), with a lower 95% confidence limit of €22 000 (determined by 5000 bootstrap samples).

Figure 3 shows the distribution of raw scores for four psychological variables during the first year after randomisation for the mild and standard treatment groups.**[A: We would normally change 'raw' to 'unadjusted', but fig 4 legend says 'adjusted'. Please**

	Mild (n=205)	Standard (n=199)	p*
IVF treatment			
Technical procedures	1083 (734)	991 (584)	0·16
Medication	1626 (1088)	1737 (1069)	0·3
Monitoring	750 (561)	576 (693)	0·006
Indirect costs	1948 (2280)	1740 (1845)	0·3
Pregnancy and neonatal period			
Medical costs	2547 (4553)	4899 (10746)	0·01
Indirect costs	379 (1177)	802 (2270)	0·03
Total costs	8333 (5418)	10 745 (11225)	0·006

Data are mean (SD). *Independent groups *t* test (assuming unequal variances). Analysis includes costs of pregnancies up to 6 weeks after delivery. Mean costs for pregnancy are across the whole group, including those who did not achieve pregnancy.

Table 4: **Total costs of IVF treatment per couple over 12 months (€)**

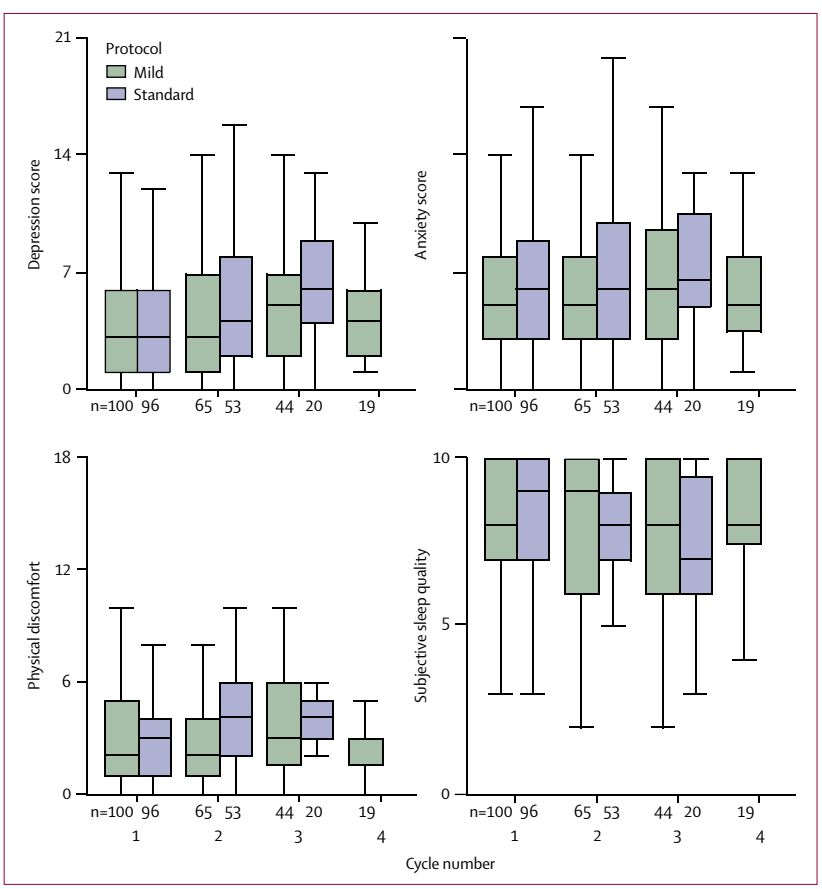

Figure 3: **Adjusted means of scores on psychological dimensions after IVF cycles in both mild and standard treatment groups. High scores represent high anxiety, depression, and physical discomfort and better subjective sleep quality.** [A: Box and whisker plots are normally used to show median, IQR and 95% CI. Does this apply to your data?]

advise.] We found no difference in non-response to questionnaires between the two groups (47% for both, p=0·8). Responders did not differ from the non-responders in age (p=0·7), duration of infertility (p=0·9), or pregnancy history (p=0·07). However, non-response was associated with cycles in which no oocytes were retrieved or no embryo could be transferred (p<0·001, p<0·001, respectively).**[A: Please give actual p value]** Non-response was not related to achievement of pregnancy (p=0·24). In a multivariate analysis, only achievement of an embryo transfer remained statistically significant. Treatment strategy was not a significant factor in this analysis (p=0·6). There were no significant differences between the two groups between the area under the curve for scores on the hospital anxiety and depression scale for anxiety (p=0·9) or depression (p = 0·8), the Hopkins symptom checklist for physical discomfort (p = 0·5), and the subjective sleep quality scale (p = 0·3).

Discussion

Our study showed that, in women younger than 38 years, the 1-year cumulative proportion of term livebirths was much the same with a mild strategy for IVF, consisting of GnRH antagonist cotreatment with single embryo transfer, as with the standard IVF strategy. Moreover, overall discomfort to patients was similar, despite an increase in the average number of IVF cycles for the group assigned mild treatment. The proportion of multiple pregnancies per couple was greatly reduced with the mild strategy, as were the overall costs per term livebirth.

Previous studies that focused on outcomes in single cycles[14,15,21] have shown that single embryo transfer in women younger than 36 years is highly effective for reduction of multiple pregnancies, but at the expense of the probability of pregnancy per cycle. Although we also noted a reduced chance of term livebirths per cycle for the mild strategy, the cumulative 1-year proportion of pregnancies that produced term livebirths was about 45% for either strategy. Therefore, the reduced chances of birth per cycle with mild IVF treatment should be considered in the context of its shorter and less costly cycles of ovarian stimulation, less risk of ovarian hyperstimulation syndrome, reduced rates of discontinuation, and increased numbers of IVF cycles in a set time. The difference between the 1-year analysis and the per-treatment-group analysis was small, illustrating that 1 year was long enough for most couples to finish the randomised strategy.**[A: Please clarify this point. Do you mean long enough to complete four cycles of the mild IVF treatment?]**

For calculation of the chance of a term livebirth per 12 months per couple, we counted every livebirth as equivalent to one child—ie, we did not count term-born twins as two livebirths.**[A: okay?]** Term-born twins could be perceived as a positive outcome—eg for parents who wanted more than one child the need for subsequent IVF treatments might be reduced. However, in addition to the distinct increase in 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.[22] Consideration of the benefits of single embryo transfer should also take account of the livebirths which might arise from the subsequent transfer of cryopreserved surplus embryos.[14] By contrast, others argue that only a singleton term livebirth is a successful outcome of IVF.[23]

We used the Kaplan-Meier method to calculate the 1-year cumulative proportion of term livebirths; this differs from standard method of censoring, which assumes that patients who drop out have a similar chance of pregnancy to patients who continue treatment.[20] Because we were able to use all information about pregnancies that happened within 1 year, we could do an intention-to-treat analysis of the true cumulative proportion of patients who achieved term livebirths, without making assumptions about pregnancy chance for those who withdrew (no censoring). The proportion of term livebirths we calculated is lower than those usually reported, since censoring masks the numbers of patients who discontinue treatment (eg, because of discomfort). Censoring is therefore not appropriate for studies with endpoints linked to treatment-related stress.

Although the mild treatment group had more IVF cycles within 1 year, overall discomfort to patients in the two groups during that year was similar. We used assessments of discomfort at the end of each IVF cycle to calculate the cumulative discomfort score over time. Although stress levels might have varied during and between treatment cycles, patients' discomfort associated with the mild strategy seemed to be stable over time, whereas the discomfort associated with standard treatment intensified during subsequent treatment cycles. The questionnaire response rate, of just 50%, was within normally reported ranges for this type of psychological assessment,[24] and did not differ between the two treatment groups (data not shown). Women who had no oocyte retrieval or no embryo transfer were significantly less likely to respond than other patients, which could have led these features to be underestimated in both treatment groups. However, this difference is unlikely to have biased the results in favour of either treatment strategy.

The potential health economic benefits of single embryo transfer have been investigated in only a few studies.[25,26] One randomised trial suggested that a single embryo transfer strategy was associated with lower total costs per cycle than cycles in which two embryos were transferred, because of the associated reduction in multiple pregnancies.[12] Despite the higher average number of cycles that are possible in 1 year with the mild strategy (and consequently the higher monitoring and indirect costs) the overall costs per term livebirth within that time were lower than those of the standard treatment strategy. Savings were mainly attributable to the reduction

in multiple pregnancies. We assessed costs for a postnatal period of only 6 weeks after the expected date of delivery, which resulted in a conservative estimate of the additional costs, since prematurity is also associated with long-term health consequences.[27]

[A: This paragraph has been moved from your introduction—okay?]Challenges to contemporary concepts of success in assisted reproduction, which emphasise single cycle outcomes, could facilitate further development of IVF.[28]**[A: okay?]** The Cochrane Menstrual Disorder and Subfertility group has proposed that success should be defined per IVF treatment period rather than per cycle.[29] The definition of success could be further refined to incorporate chances for term livebirth (or healthy child) per IVF treatment period (which could include several cycles) in relation to cost, patients' discomfort, and risks of complications.

Our findings emphasise the medical, health, economic, and psychological benefits of mild IVF strategies in women younger than 38 years. However, if this mild IVF treatment strategy is to be widely implemented, IVF outcomes should be redefined in broader terms that encompass the interests of the couple, the child, and even the providers of health care. In other medical specialties, such as oncology, normal practice is to present success of a treatment strategy as survival per time period.[30] . The chance that IVF can produce a healthy baby (or babies) needs to be weighed against the discomfort and risks of complications and costs associated with the treatment. Adoption of the endpoint of term-delivery per time period (which might consist of several IVF cycles) would encourage patient-friendly stimulation protocols and single embryo transfer. In conclusion, our findings should encourage more widespread use of mild ovarian stimulation and single embryo transfer in clinical practice. However, adoption of our mild IVF treatment strategy would need to be supported by counselling of both patients and health-care providers to redefine IVF success and explain the risks associated with multiple pregnancies[31] and by institution of reimbursement systems that encourage, rather than penalise, the practice of single embryo transfer.[32]

Contributors

E M E W Heijnen, M J C Eijkemans, J Passchier, E R Te Velde, N S Macklon, and B C J M Fauser cooperated to design the study. All authors participated in the collection, analysis, and interpretation of data. E M E W Heijnen was principally responsible for writing the paper, and all authors have seen and approved the final version.

Conflict of interest statement

E M E W Heijnen started work as a clinical research scientist at NV Organon, Oss, Netherlands, after finishing this research. The other authors have no conflicts of interest.

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