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ORIGINAL ARTICLE *Infertility*

A mild ovarian stimulation strategy in women with poor ovarian reserve undergoing IVF: a multicenter randomized non-inferiority trial

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STUDY QUESTION: In subfertile women with poor ovarian reserve undergoing IVF does a mild ovarian stimulation strategy lead to comparable ongoing pregnancy rates in comparison to a conventional ovarian stimulation strategy?

SUMMARY ANSWER: A mild ovarian stimulation strategy in women with poor ovarian reserve undergoing IVF leads to similar ongoing pregnancy rates as a conventional ovarian stimulation strategy.

WHAT IS KNOWN ALREADY: Women diagnosed with poor ovarian reserve are treated with a conventional ovarian stimulation strategy consisting of high-dose gonadotropins and pituitary downregulation with a long mid-luteal start GnRH-agonist protocol. Previous studies comparing a conventional strategy with a mild ovarian stimulation strategy consisting of low-dose gonadotropins and pituitary downregulation with a GnRH-antagonist have been under powered and their effectiveness is inconclusive.

STUDY DESIGN, SIZE, DURATION: This open label multicenter randomized trial was designed to compare one cycle of a mild ovarian stimulation strategy consisting of low-dose gonadotropins (150 IU FSH) and pituitary downregulation with a GnRH-antagonist to one cycle of a conventional ovarian stimulation strategy consisting of high-dose gonadotropins (450 IU HMG) and pituitary downregulation with a long mid-luteal GnRH-agonist in women of advanced maternal age and/or women with poor ovarian reserve undergoing IVF between May 2011 and April 2014.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Couples seeking infertility treatment were eligible if they fulfilled the following inclusion criteria: female age ≥35 years, a raised basal FSH level >10 IU/ml irrespective of age, a low antral follicular count of ≤5 follicles or poor ovarian response or cycle cancellation during a previous IVF cycle irrespective of age. The primary outcome was ongoing pregnancy rate per woman randomized. Analyses were on an intention-to-treat basis. We randomly assigned 195 women to the mild ovarian stimulation strategy and 199 women to the conventional ovarian stimulation strategy.

MAIN RESULTS AND THE ROLE OF CHANCE: Ongoing pregnancy rate was 12.8% (25/195) for mild ovarian stimulation versus 13.6% (27/199) for conventional ovarian stimulation leading to a risk ratio of 0.95 (95% CI: 0.57–1.57), representing an absolute difference

of −0.7% (95% CI: −7.4 to 5.9). This 95% CI does not extend below the predefined threshold of 10% for inferiority. The duration of ovarian stimulation was significantly lower in the mild ovarian stimulation strategy than in the conventional ovarian stimulation strategy (mean difference −1.2 days, 95% CI: −1.88 to −0.62). Also, a significantly lower amount of gonadotropins was used in the mild simulation strategy, with a mean difference of 3135 IU (95% CI: −3331 to −2940).

LIMITATIONS, REASONS FOR CAUTION: A limitation of our study was the lack of data concerning the cryopreservation of surplus embryos, so we are not informed on cumulative pregnancy rates. Another limitation is that we were not able to follow up on the ongoing pregnancies in all centers, so we are not informed on live birth rates.

WIDER IMPLICATIONS OF THE FINDINGS: The results are directly applicable in daily clinical practice and may lead to considerable cost savings as high dosages of gonadotropins are not necessary in women with poor ovarian reserve undergoing IVF. A health economic analysis of our data planned to test the hypothesis that mild ovarian stimulation strategy is more cost-effective than the conventional ovarian stimulation strategy is underway.

STUDY FUNDING/COMPETING INTEREST(S): This study was supported by NUFFIC scholarship (the Netherlands) and STDF short-term fellowship (Egypt).

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Key words: mild ovarian stimulation / poor ovarian reserve / randomized / GnRH antagonist / gonadotropins

Introduction

The mean age of women giving birth to their first child in developed countries is still rising (Schmidt *et al.*, 2005; Rashad *et al.*, 2005; Martin *et al.*, 2006). As a result, more women face subfertility due to diminished ovarian function who then seek medical help to become pregnant (te Velde and Pearson, 2002). IVF is now the treatment of choice in older women and it is estimated that 37% of all IVF cycles are performed in older women (NICE guidelines, 2013; Kupka *et al.*, 2014).

Poor ovarian reserve is a negative prognostic factor for success in IVF (van Loendersloot *et al.*, 2010; Broer *et al.*, 2013). Data from ART-registers in the UK, Canada and Egypt showed live birth rates per started cycle of 11.1%, 11.4% and 6.7%, respectively, in women with poor ovarian reserve (Serour *et al.*, 2010; Sunkara *et al.*, 2011; Gunby *et al.*, 2011).

Various stimulation protocols have been introduced to improve pregnancy outcomes in these women. Traditionally, the stimulation protocol for women with poor ovarian reserve includes high doses of FSH or HMG—up to 600 IU/day—which is very costly, but recently, protocols with low dosages of gonadotropines have been introduced (Shanbhag *et al.*, 2007; Schimberni *et al.*, 2009; Masschaele *et al.*, 2012). Several studies have compared mild ovarian stimulation consisting of low doses of gonadotropins or gonadotropins and co-treatment by oral compounds with high doses of gonadotropins in IVF cycles (Cedrin-Durnerin *et al.*, 2000; D'Amato *et al.*, 2004; Goswami *et al.*, 2004; Morgia *et al.*, 2004; Klinkert *et al.*, 2005; Kim *et al.*, 2009; Berkkanoglu and Ozgur, 2010; Madani *et al.*, 2012; Hu *et al.*, 2014). These studies were either small randomised controlled trials, not powered to detect a difference in ongoing pregnancy rates or were retrospective studies and do not allow for definite conclusions. We therefore designed a large multicenter randomized clinical trial to compare the effectiveness of a mild ovarian stimulation strategy versus a conventional ovarian stimulation strategy in terms of ongoing pregnancy rate.

Materials and Methods

We performed a multinational, multicenter, open label, two arm, parallel group, randomized controlled non-inferiority trial in five fertility centers. Full details of the trial protocol can be found at www.studiesobsgyn.nl/prima. The protocol was designed at the Academic Medical Center in the Netherlands and the trial was conducted in several centers in Iran, Egypt and Syria between May 2011 and April 2014.

Couples seeking infertility treatment were eligible if they fulfilled one of the following inclusion criteria: female age ≥35 years, a raised basal FSH level >10 IU/ml irrespective of age, a low antral follicular count of <5 follicles or poor ovarian response or cycle cancellation during a previous IVF cycle irrespective of age. We defined poor ovarian response in a previous cycle as an oocyte yield ≤5 (Ferraretti *et al.*, 2011). Exclusion criteria were pre-existing medical conditions, female age >43 years, congenital uterine anomalies, polycystic ovary syndrome and any other causes for anovulation.

Couples were randomly allocated in a 1:1 ratio to receive either 150 IU of FSH in a GnRH antagonist cycle or 450 IU of HMG in a mid-luteal long GnRH-agonist protocol. Randomization was performed with an online randomization program, stratified for study center. A web-based program generated a unique number with allocation code after entry of the patient's initials and date of birth. Neither the recruiters nor the trial project group could access the randomization sequence. Blinding was not possible owing to the nature of the interventions.

In women allocated to the mild ovarian stimulation strategy, pretreatment with an oral contraceptive pill was followed by ovarian stimulation starting with a fixed daily dose of 150 IU/day FSH (Gonal-F®, Merck Serono, Geneva, Switzerland or Fostimon, IBSA, Lodi, Italy) on Day 5 after the last oral contraceptive pill and after establishing ovarian and uterine quiescence using transvaginal ultrasound. On stimulation Day 6, 0.25 mg/day s.c. of a GnRH antagonist (Cetrotide®, Merck Serono or Orgalutran® MSD, Haar, Germany) was commenced. Ovulation was triggered by 10 000 IU human chorionic gonadotropin hormone (Pregnyl, Schering-Plough Organon, Oss, the Netherlands) when a leading follicle reached 18 mm, and follicle aspiration was done by transvaginal ultrasound guided oocyte retrieval 34–36 h

thereafter. Cycles were canceled when there were no ovarian response or <2 follicles <15 mm after 7 days of ovarian stimulation.

Subsequently, embryo transfers were performed according to the local policy of participating centers and two top-quality embryos were transferred on Day 3. Transfer of >2 embryos was allowed when the women were >40 years old or had poor embryo quality. The morphological score, the cell number, degree of fragmentation of the embryo and the uniformity of the blastomeres were assessed daily. The embryos were given a score of 1 (no fragmentation), 2 (<20% fragmentation), 3 (20–50% fragmentation) or 4 (>50% fragmentation) (Puissant *et al.*, 1987). Top-quality embryos were defined as embryos of Scores 1 and 2 and poor-quality embryos were defined as embryos of Scores 3 and 4. Embryo transfer took place on Day 3 after fertilization. Any remaining top-quality embryos were cryopreserved and transferred after thawing in subsequent cycles until pregnancy was achieved or all embryos had been transferred. Luteal phase support was with progesterone suppositories (Cyclogest ®200 mg, Actavis, Barnstaple, UK, three times daily) or intramuscular administration progesterone, starting on the day of follicle aspiration until a urine pregnancy test 17 days later. In case of a positive pregnancy test, women were monitored with transvaginal ultrasound at 5–6 weeks of amenorrhea to check whether an intrauterine gestational sac was present. Subsequently, monitoring took place at 11–12 weeks amenorrhea to register the presence of an intrauterine gestational sac with fetal heartbeat.

In the women allocated to the conventional ovarian stimulation strategy, daily injections were given of 0.1 mg s.c of a gonadotropin releasing hormone agonist to prevent premature ovulation (Decapepetyl®, Ferring, Parsippany, NJ, USA or Lucrin ®; Abbott, Osaka, Japan) followed by stimulation with fixed daily injections of 450 IU HMG (Menopur®, Menogon® Ferring or Merional®, IBSA). Ovulation was triggered by 10 000 IU human chorionic gonadotropins hormone (Pregnyl, Schering-Plough Organon) when a leading follicle reached 18 mm and follicle aspiration was done by transvaginal ultrasound guided oocyte retrieval 34–36 h thereafter. The remainder of the cycle was identical to the mild ovarian stimulation strategy.

The primary outcome was ongoing pregnancy rate per randomized woman. An ongoing pregnancy was defined as a viable pregnancy of at least 10–12 weeks of gestation.

Secondary outcomes included clinical pregnancy (any registered embryonic heartbeat at sonography), biochemical pregnancy (an increase in serum HCG or a positive pregnancy test), multiple pregnancy (registered heartbeat of at least two foetuses at 6–8 weeks of gestation), early pregnancy loss (loss of pregnancy before 12 weeks of gestations), number of oocytes retrieved, number of metaphase II oocytes, fertilization rate, number of embryos obtained, number of embryo transfers, total FSH/HMG doses used for ovarian stimulation, cancellation rate and drop-out rate.

Ethical approval

All participants gave written informed consent. The study protocol was approved by the local ethics committee at each participating center and was registered before its start with Clinical trials identifier: NTR2788 (http://www.trialregister.nl/trialreg/admin/rctview).

Statistical analysis

The trial was designed to determine whether the mild ovarian stimulation strategy was non-inferior to the conventional ovarian stimulation strategy, with a predefined non-inferiority margin of 10%, meaning that the upper boundary of the 95% CI of the absolute difference between the primary endpoint in the two study groups would be lower than 10%. We determined the sample size on the basis of an expected ongoing pregnancy rate in the conventional strategy group of 20%. On basis of the Chi-square statistic and calculating with 80% power to detect the predefined non-inferiority margin at a one-sided α level of 0.05; we would need 177 women in each study group. Assuming a loss to follow up of 10%, the total study population was set at 394 people (197 per arm).

All randomized patients were included in all analyses according to the intention-to-treat principle. We performed an additional per protocol analysis for our primary outcome. We estimated differences in the binary outcomes as relative risks with 95% CIs using Fisher exact or Chi-square as appropriate. For continuous outcomes, we calculated means and SDs or medians with ranges and we evaluated differences with Mann–Whitney *U*-tests. We used SPSS (version 20.0, http://ibm-spss-statistics.com) for all statistical analyses.

Results

Between May 2011 and April 2014, we included 394 couples; 195 couples were assigned to the mild ovarian stimulation strategy and 199 to the conventional ovarian stimulation strategy. Eleven women did not receive the allocated intervention and 15 women were lost to follow up (Fig. 1). Baseline characteristics in the two groups were similar in the two groups (Table I).

Pregnancy outcomes are listed in Table II. The primary outcome ongoing pregnancy was 12.8% (25/195) for women who received the mild ovarian stimulation strategy and 13.6% (27/199) for women who received the conventional ovarian stimulation strategy (risk ratio, RR 0.95; 95% CI: 0.57–1.57), representing an absolute difference of −0.7% (95% CI: −7.4 to 5.9). This 95% CI does not extend below the predefined threshold of 10% for inferiority. Using a per protocol analysis, in the mild ovarian stimulation strategy eight women did not start treatment and eight women dropped out or were lost to follow up—this number was 10 in the conventional ovarian stimulation strategy, three women did not start treatment and seven women dropped out or were lost to follow up. The ongoing pregnancy rate was 14.0% (25/179) versus 14.3% (27/189) leading to a RR of 0.98 (95% CI: 0.59–1.62), representing an absolute difference of −0.3% (95% CI: −7.4 to 6.8). This 95% CI does not extend below the predefined threshold of 10% for inferiority.

Using logistic regression, we have evaluated the interaction for female age below and above 35 years of age and ongoing pregnancy rate. In women below 35 years of age, there were 11 ongoing pregnancies in 61 women in the mild ovarian stimulation strategy and 12 ongoing pregnancies in 66 women in the conventional ovarian stimulation strategy (RR: 0.99; 95% CI: 0.47–2.0). In women above 35 years of age, there were 14 ongoing pregnancies in 132 women in the mid ovarian stimulation strategy and 15 ongoing pregnancies in 130 women in the conventional ovarian stimulation strategy (RR: 0.91; 95% CI: 0.45–1.81). There was no indication for interaction ($P = 0.79$).

We found no evidence of any differences in rates of clinical pregnancy [15.3% (30/195) vs 15.5% (31/199)] (RR 0.86; 95% CI: 0.55–1.34), early pregnancy loss [16.6% (5/30) vs 12.9% (4/31)] (RR 1.20; 95% CI: 0.36–4.17), twin pregnancies [10% (3/30) vs 22.5% (7/31)] (RR 0.41; 95% CI: 0.10–1.65) and biochemical pregnancy [20% (39/195) vs 18% (36/199)] (RR 1.10; 95% CI: 0.66–1.84). One ectopic pregnancy occurred in each intervention arm.

Ovarian stimulation and laboratory outcomes are shown in Table III. The duration of ovarian stimulation was significantly lower in the mild ovarian stimulation strategy (8.42 ± 2.89) compared with the conventional ovarian stimulation strategy (9.67 ± 3.10) with a mean difference

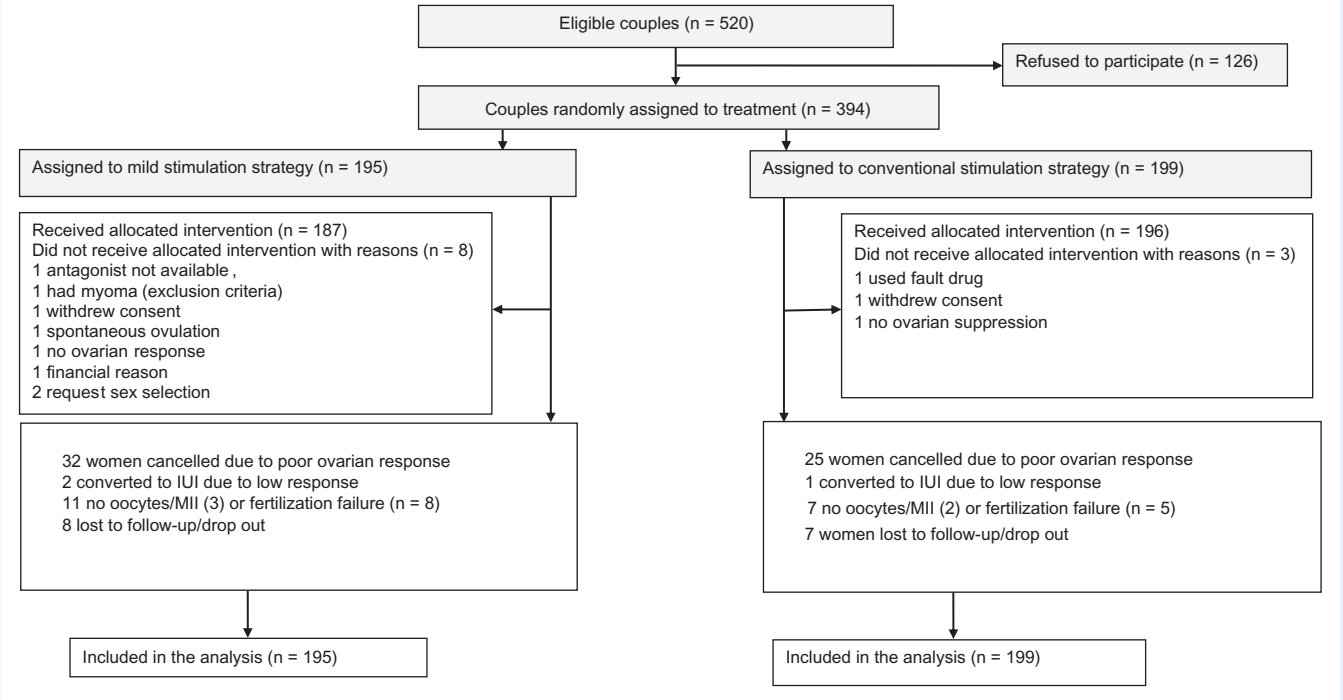

Figure 1 Eligibility, randomization and follow-up.

Table I Baseline characteristics of the couples[a].

	Mild ovarian stimulation strategy (*N* = 195)	Conventional ovarian stimulation strategy (*N* = 199)
Age of female partner (years)	36.5 ± 3.9	36.6 ± 4.3
Body mass index (kg/m^2)	27.2 ± 4.4	27.5 ± 5.3
AFC	5.3 ± 1.6	6.4 ± 2.9
Basal FSH (IU/l)	11.4 ± 4.3	10.5 ± 4.0
Basal estradiol (pg/ml)	43.8 ± 22.6	42.8 ± 25.7
AMH[b] (ng/ml)	0.5 ± 0.6	0.6 ± 0.6
Median (IQR)[c] duration of time attempting to conceive (years)	9.0 (6.0–13)	8.5 (4.0–13.2)
Primary infertility, *n* (%)	143 (73)	138 (70)
Previous IVF/ICSI cycles, *n* (%)	89 (45)	94 (48)

[a]Plus–minus values are means ± SD.
[b]AMH, anti-müllerian hormone. AMH was measured in *n*/*N* (%) of the patients.
[c]Interquartile range.

of −1.2 days (95% CI: −1.88 to −0.62). Also a significantly lower amount of gonadotropins was used in the mild ovarian simulation strategy, with a mean difference of −3135 IU (95% CI: −3331 to −2940).

In the mild ovarian stimulation strategy, 52 (26%) cycles were canceled and 37 (18%) cycles in the conventional ovarian stimulation strategy (RR 1.5; 95% CI: 0.96–2.5). The mild ovarian stimulation strategy resulted in significantly fewer retrieved oocytes compared with the conventional ovarian stimulation strategy (mean: 3.3, 95% CI: 2.3–4.0 vs 5.0, 95% CI: 4.3–5.5), fewer mature oocytes (MII) (mean: 2.7, 95% CI: 2.4–3.2 vs 4, 95% CI: 3.4–4.5), fewer fertilized oocytes (mean: 2.4, 95% CI: 2.1–2.8 vs 3.4, 95% CI: 2.8–3.8) and fewer embryos (mean: 2.0, 95% CI: 1.8–2.5 vs 2.7, 95% CI: 2.3–3) but the number of good quality embryos (mean: 0.8, 95% CI: 0.6–1.0 vs 0.8, 95% CI: −0.6 to 1.1) and embryos transferred (mean: 0.8, 95% CI: 0.6–1.0 vs 0.8, 95% CI: 0.6–0.9) were similar.

Discussion

In this clinical trial, involving women with poor ovarian reserve, a mild ovarian stimulation strategy did not lead to less ongoing pregnancies

Table II Pregnancy outcomes.

Outcome	Mild ovarian stimulation strategy (*N* = 195)	Conventional ovarian stimulation strategy (*N* = 199)	RR (95% CI)
Ongoing pregnancy ≥12 weeks, no. of women (%)	25 (12.8)	27 (13.6)	0.95 (0.57–1.57)
Clinical pregnancy, no. of women (%)	30 (15.3)	31 (15.5)	0.86 (0.55–1.34)
Early pregnancy loss, no. of women/total no. of clinical pregnancies (%)	5 (16.6)	4 (12.9)	1.20 (0.36–4.17)
Twin pregnancy, no. of women/total no. of clinical pregnancies (%)	3 (10)	7 (22.5)	0.41 (0.10–1.65)
Biochemical (positive βhCG), no. of women (%)	39 (20)	36 (18)	1.10 (0.66–1.84)

Table III Ovarian stimulation and laboratory outcomes.

Outcome	Mild ovarian stimulation strategy (*N* = 195)	Conventional ovarian stimulation strategy (*N* = 199)	RR (95% CI)	MD (95% CI)
Duration of ovarian stimulation (days)	8.4 ± 2.9	9.7 ± 3.1		−1.2 (−1.88 to −0.62)
Total amount of gonadotropins (IU)	1436 ± 552	4472 ± 1156		−3135 (−3331 to −2940)
Cycle cancellation, no. (%)	52 (26.6)	37 (18.6)	1.5 (0.96–2.5)	
No. oocytes retrieved (median)	3.3 ± 3.5 (2) (95% CI: 2.3–4)	5.0 ± 4 (4) (95% CI: 4.3–5.5)		−1.6 (−2.5 to −0.89)
No. MII oocytes (median)	2.7 ± 2.6 (2) (95% CI: 2.4–3.2)	4.0 ± 3.6 (3) (95% CI: 3.4–4.5)		−1.3 (−2.0 to −0.69)
No. fertilized oocytes	2.4 ± 2 (95% CI: 2.1–2.8)	3.4 ± 3 (95% CI: 2.8–3.8)		−1.0 (−1.6 to −0.47)
No. embryos obtained (median)	2.0 ± 1.9 (2) (95% CI: 1.8–2.5)	2.7 ± 2.4 (2) (95% CI: 2.3–3)		−0.72 (−1.2 to −0.22)
No. top-quality embryos (median)	0.8 ± 1.1 (0.00) (95% CI: 0.6–1.0)	0.8 ± 1.2 (0.00) (95% CI: 0.6–1.1)		−0.08 (−0.41 to 0.24)
No. embryos transferred (median)	0.8 ± 1.3 (2) (95% CI: 0.6–1.0)	0.8 ± 1.2 (2) (95% CI: 0.6–0.9)		−0.19 (−0.48 to 0.09)

Plus–minus values are means ± SD

compared with a conventional ovarian stimulation strategy, but the mild ovarian stimulation strategy yielded a nearly 3000 IU reduction in use of gonadotropins per woman. We found no differences in ovarian stimulation results such as number of embryos transferred and their quality, except for a lower number of retrieved oocytes, MII oocytes, fertilized oocytes and embryos obtained in the mild ovarian stimulation strategy.

The strength of this study lies in the comparison between two strategies of ovarian stimulation in women with poor ovarian reserve in a well powered and large multicenter international RCT with central randomization comparing, for the first time, the lowest dose of FSH ever used in a GnRH antagonist protocol, with conventional ovarian stimulation with high dosages of 450 IU of HMG. In addition, the dose of the gonadotropins was not increased or decreased throughout the stimulation phase. We achieved excellent success rates with this strategy in women traditionally associated with poor reproductive outcome, casting reasonable doubt on the utility of high doses of gonadotropins (Land *et al.*, 1996).

The choice of our strategies may warrant some discussion. The whole purpose of the trial was not to simply compare two dosages of FSH, but to compare the best and clinically most relevant strategies, in which one strategy would use less gonadotropin than currently customary in women with poor ovarian reserve.

To achieve the best possible mild ovarian stimulation strategy, we chose dual pituitary suppression for our mild ovarian stimulation strategy, because pretreatment with oral contraceptive pills in GnRH antagonist protocols has been proven to achieve better scheduling of the stimulation cycle, to prevent early endogenous FSH rise, to reduce the amount and duration of gonadotropins required for follicular maturation, to improve follicular homogeneity and to generate chromosomally normal embryos by reduced interference with ovarian physiology (Van Blerkom and Davis, 2001; Huirne *et al.*, 2006; Baart *et al.* 2007).

To achieve the best possible conventional ovarian stimulation strategy, we used HMG since the addition of an LH-like component to FSH

in a long GnRH agonist protocol may increase ongoing pregnancy rates especially in women with poor ovarian reserve (Mochtar *et al.*, 2007).

Although we designed our study protocol before the release of Bologna criteria, when there was no consensus on the definition of women with poor ovarian reserve or poor ovarian response, our women post hoc do fulfill the Bologna criteria, which reduces bias caused by spurious definitions of poor responders, allowing to draw reliable conclusions (Ferraretti *et al.*, 2011). The trial was further strengthened by our primary outcome, the ongoing pregnancy rate.

A limitation of our study was the lack of data concerning the cryopreservation of surplus embryos, so we are not informed on cumulative pregnancy rates. Another limitation is that we were not able to follow up on the ongoing pregnancies in all centers, so we are not informed on live birth rates, but, recently published data shown that individualized gonadotropin dosing in predicted poor responders does not influence live birth rates or time to pregnancy, instead of the higher number of oocytes retrieved (Tilborg *et al.*, 2016). Open label nature of the study could be considered as a source of bias. Blinding was not possible for the type of intervention, but we consider it unlikely that blinding would affect pregnancy outcome for the comparisons under study.

Furthermore, the different downregulation protocols—GnRH antagonist versus long GnRH agonist—could be considered to represent a flaw in the study design. Three meta-analyses compared GnRH antagonist with GnRH agonist protocols in poor responders and showed no differences in the number of retrieved oocytes, mature oocytes, cycle cancellation rate or clinical pregnancy rate or pregnancy rate (Al-Inany *et al.*, 2011; Pu *et al.*, 2011; Xiao *et al.* 2013).

Our results are contributing more data in the form of a RCT to existing information and are in line with three randomized clinical trials that evaluated mild ovarian stimulation in women with poor ovarian reserve (Klinkert *et al.*, 2005; Revelli *et al.*, 2014; Bastu *et al.*, 2016). The first study entailed 52 women with antral follicle count (AFC) <5 follicles before starting their first IVF cycle, and compared 150 IU of FSH to a fixed daily dose of 300 IU FSH (Klinkert *et al.*, 2005). The second study entailed 695 women with expected poor ovarian response and compared a mild stimulation protocol 100 mg/day Clomiphene citrate followed by 150 IU HMG combined with a GnRH antagonist to a conventional stimulation protocol with daily 300 IU HMG combined with a GnRH agonist (Revelli *et al.*, 2014). There was no difference in ongoing pregnancy rates, but there were more oocytes and embryos in the conventional strategy. In the third RCT, entailing 95 women, found no difference in pregnancy rates between women receiving 150 FSH/HMG combined with letrozole in a fixed GnRH antagonist protocol and women receiving either 300 or 450 IU FSH/HMG (Bastu *et al.*, 2016).

When applied in daily clinical practice, the data generated by this trial may lead to considerable cost savings as high dosages of gonadotropins are not necessary in women with poor ovarian reserve undergoing IVF. A cost effectiveness analysis to prove or refute this hypothesis is underway.

In conclusion, a mild ovarian stimulation strategy is non-inferior to conventional ovarian stimulation in terms of the ongoing pregnancy rates and is associated with shorter duration of stimulation, lower amount of gonadotropins and less costs required for ovarian stimulation. Thus, mild ovarian stimulation should be the treatment of choice in women with poor reserve undergoing IVF.

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Authors' roles

M.A.Y., M.v.W., H.A.-I., M.H.M. and F.v.d.V. initiated and conceptualized the protocol. M.A.Y., T.M., N.J., S.K., A.R., M.A., M.A., S.A., R.T., L.Z., M.E.-M., E.S. and M.K. undertook patient recruitment and data collection, M.A.Y. and M.v.W. performed the analyses of the data. All authors participated in the interpretation of the data and writing of the final version.

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Conflict of interest

None declared.

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