

## Original Research Articles

# Increased gonadotropin dosing (375 vs 225 IU/day) does not improve clinical outcomes in poor-prognosis patients undergoing IVF: results of a multi-center randomized controlled trial

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### Objective

Is the use of higher gonadotropin dosing associated with improved clinical pregnancy rate (CPR), live birth rate (LBR) and cumulative live birth rate (cLBR) in expected poor responders undergoing IVF?

### Design

Prospective, randomized, controlled trial of women between the ages of 18–42 years meeting POSEIDON 3 or 4 criteria (low ovarian reserve) in 6 Hungarian IVF centers. Eligible women were randomly assigned to stimulation using a fixed lower (225 IU: 150 IU recombinant follicle stimulating hormone (FSH) + 75 IU human menopausal gonadotropin (hMG)) or higher (375 IU: 225 IU recombinant FSH + 150 IU hMG) dose gonadotropin treatment following an antagonist protocol. Stimulation, embryology and clinical outcomes were compared.

### Results

190 women were randomized; 185 started treatment (intention-to-treat population) and 133 underwent embryo transfer (as treated population). The groups were well-balanced regarding demographic parameters. Significantly lower dose gonadotropin was used in the low dose arm (2189 IU vs 3550 IU,  $p < 0.001$ ). None of the clinical outcome parameters, including the cLBR (18.1% vs 14.4%,  $p = 0.48$ ) were significantly different. When outcomes based on the different follitropin preparations (FSH- $\alpha$  and FSH- $\delta$ ) were evaluated, the clinical outcomes appeared superior in the lower dose groups. Still, none of the differences reached statistical significance.

### Conclusion

This exploratory analysis did not observe any benefit from administering higher doses of gonadotropin in poor responder patients, though the study was underpowered to detect small to moderate differences.

## BACKGROUND

A well-executed cycle stimulation that optimizes the oocyte yield correlates with the success of *in vitro* fertilization (IVF).<sup>1,2</sup> Urinary and recombinant gonadotropins are used

in a personalized way with age, ovarian reserve markers, body mass index (BMI) and response to previous stimulation considered to achieve the stimulation goals.<sup>3</sup> Based on these parameters, patients are often identified as expected normal, hyper or poor responders.

With respect to poor responders, various treatment protocols have been evaluated to optimize oocyte yield.<sup>4</sup> Most of these protocols involve the use of increased dose gonadotropins, which is based on outcomes of gonadotropin dose finding studies where more follicles and oocytes are obtained as the gonadotropin dose is increased.<sup>5</sup> However, this practice fails to follow the same trend in the number of embryos and good quality blastocysts.<sup>2,5</sup>

Recent ESHRE guidelines question the benefit of gonadotropin doses exceeding 300 IU daily,<sup>3</sup> yet clinical practice often employs doses of 450-600 IU in poor responders, highlighting the disconnect between evidence and practice. Several randomized controlled trials (RCT) have compared clinical outcomes using a lower versus a higher dose of gonadotropin in poor responder patients<sup>6-13</sup> but have a number of inconsistencies, including the varying criteria to identify poor responders, the use of different stimulation protocols (antagonist vs long protocols), the use of oral agents where international unit conversion is not possible, dose escalation during cycles, and inconsistent primary endpoints, making meta-analysis and clinical application challenging.<sup>14</sup> More recently, POSEIDON and Bologna criteria have emerged as standard tools to identify poor responders.<sup>15,16</sup> Beyond clinical outcomes, the economic implications of high-dose protocols are substantial, with gonadotropin costs representing a significant portion of IVF treatment expenses, particularly relevant for patients who may require multiple cycles.

Therefore, the aim of our RCT was to compare clinical outcomes, including live birth rate (LBR) and cumulative (c)LBR, using a lower versus a higher dose gonadotropin regimen in expected poor responders by POSEIDON criteria.

## METHODS

This multicenter RCT took place in six IVF centers in Hungary. IRB approval was obtained prior to study start (52007-16/2021/EÜIG) and the study was conducted in accordance with the principles set forth in the [Helsinki Declaration](#) and local regulations. The trial was registered at Clinical Trials (NCT05103228; October 21, 2021). All study sites were required to obtain an additional insurance policy to cover the clinical trial as per local regulations. Recruitment was initiated in December 2021 with complete recruitment expected within one year. Due to slow enrollment, the recruitment period was eventually extended until July 2023 at which point the study was closed out due to lack of funding for insurance extension. Frozen embryo transfers resulting from the fresh cycles were included up until the end of 2023 and pregnancy outcome data was collected up until September 2024. All participants were given a detailed explanation of the study goals, methods and potential disadvantages, and were required to sign an informed consent prior to enrollment.

## INCLUSION-EXCLUSION

The inclusion-exclusion criteria are shown in [Table 1](#). None of the cycles involved pre-implantation genetic testing (PGT) for aneuploidy as it is not allowed by Hungarian law.

## RANDOMIZATION

Enrollment into the study was performed prior to gonadotropin stimulation. Eligible participants were randomly assigned to their treatment protocol based on an on-line randomization list that was generated prior to the start of the trial ([www.randomizer.org](http://www.randomizer.org)). Patients were randomized to either a lower vs. higher dose of gonadotropins and to Follitropin- $\alpha$  or  $\delta$  use. Follitropin- $\alpha$  and  $\delta$  have been shown to result in similar clinical outcomes and comparable doses of follitropins (150 IU FSH- $\alpha$  or the equivalent dose of 10  $\mu$ g FSH- $\delta$ ) were used in the lower (LD) and higher (HD) dose groups.<sup>17,18</sup> Randomization was performed by the local principal investigator (PI) once consent was obtained. Only the PI had access to the randomization list and provided the treatment allocation to his/her colleagues once the patient has signed consent and was ready to enter the study. Patients were only enrolled once regardless of their treatment outcome. Neither patients nor the providing physician were blinded to the treatment assignment.

## SAMPLE SIZE

To determine the sample size needed, we assumed a 20% clinical pregnancy rate (CPR) in our patient population that fit the inclusion criteria based on the results provided by the participating clinics. Given that we expected a greater oocyte yield in the higher dose group with greater available embryos and the potential for more embryo transfers. As such, we anticipated a 50% increase in cumulative (c)CPR and with an expected 20% dropout rate for low response and cycle cancellation, 350 participants per study arm were needed to achieve a power of 80% and an alpha error of 5%, to show superior results with the high dose FSH treatment.

Due to recruitment challenges and early study termination, the final enrollment of 190 patients was substantially below our target of 750 participants. This severe underpowering transformed our study from a definitive efficacy trial into an exploratory analysis.

## TREATMENT

Patients were randomly assigned to a lower (225 IU/day; 150 IU FSH + 75 IU hpHMG) or a higher dose (375 IU/day, 225 IU FSH + 150 IU hpHMG) gonadotropin combination and the use of Follitropin- $\alpha$  or  $\delta$ . Stimulation was started on day 2 or 3 of a spontaneous cycle or on the 5<sup>th</sup> day after contraceptive pill use. Both follitropin- $\alpha$  (FSH- $\alpha$ : Gonal-F, Merck Serono; Ovaleap, Theramex Ireland Ltd; Bemfola, Richter Gedeon Nyrt.) and follitropin- $\delta$  (FSH- $\delta$ : Ferring Pharmaceuticals) were used in combination with highly purified human menopausal gonadotropin (hpHMG: Meriofert, IBSA Farmaceutici Italia Srl). ([Figure 1](#)) The drug dose had to be maintained throughout the study unless

**Table 1. Inclusion-exclusion criteria.**

| Inclusion criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Exclusion criteria                                                                                                                                                                                                                                                                                                                                                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>Age 18-42 years</li> <li>Indication for in vitro fertilization treatment (tubal factor, male factor, low ovarian reserve, endometriosis, unexplained infertility)</li> <li>Expected poor responder based on:<br/>AMH: 0.3-1.2 ng/ml or AFC &lt;5, OR<br/>AMH&gt;1.2 ng/ml or AFC≥5 but the retrieval of ≤ 4 oocytes during previous IVF treatment (POSEIDON 3-4)*</li> <li>no more than 3 previous failed IVF cycles (if the patient had 2 or more previous cycles cancelled for poor response she cannot be included)</li> <li>regular 24-35 day cycles</li> <li>BMI: 18-35 kg/m<sup>2</sup></li> <li>intact uterine cavity</li> <li>motile sperm with normal morphology obtained from the ejaculate of testicular biopsy</li> </ul> | <ul style="list-style-type: none"> <li>Age &lt; 18 or &gt;42 years</li> <li>planned preimplantation genetic testing of the embryos</li> <li>planned elective cryopreservation</li> <li>positive HIV, hepatitis B, C screening tests</li> <li>presence of hydrosalpinx</li> <li>lack of consent</li> <li>not meeting the inclusion ovarian reserve criteria</li> </ul> |

\*POSEIDON classification according to REF 16. AMH: anti-Müllerian hormone; AFC: antral follicle count; BMI: body mass index.

there was evidence of hyper-response (estradiol [E2] level >4000 pmol/l on day 6 of stimulation or >15 follicles over 10 mm on any day of stimulation) in which case a dose reduction or cycle cancellation could be considered.

Vaginal ultrasound and serum hormone measurements were used to monitor response to stimulation from day 5-6 of stimulation and every 2-3 days thereafter. Gonadotropin releasing hormone antagonist (GnRH-ant, Cetrotide, Merck-Serono, Ganirelix, Richter Gedeon Nyrt.) was started once the lead follicle reached 12-14 mm in diameter. When the largest follicle reached >17 mm, human chorionic gonadotropin (hCG; Ovitrelle, Merck-Serono) or in the case of hyper-response GnRH agonist (0.2 mg Gonapeptyl, Ferring Pharmaceuticals Ltd) trigger was given, followed by the transvaginal, ultrasound-guided retrieval 35-36 hours later. Cycles in which there was no response to stimulation (no follicles over 10 mm after 10 days of stimulation) were cancelled. Retrieved oocytes were fertilized by conventional insemination or ICSI fertilization. In cycles with a preovulatory progesterone rise (progesterone at last scan >1.5 ng/ml), elective cryopreservation was recommended. One or two embryos were transferred (ET) transcervically under ultrasound guidance using soft catheters (Wallace, Smith Medical International Ltd., UK) after 3-5 days of group culture. The number of embryos transferred was based on local protocols and an agreement between the couple and the physician. Surplus good quality embryos were vitrified.

The luteal phase was supported with vaginal (Utrogestan, Lab Besins International SA or Cyclogest, Richter Gedeon Nyrt.) or subcutaneous (s.c., Prolutex, IBSA Farmaceutici Italia Srl) progesterone starting the day after the retrieval. Pregnancy was confirmed by serum  $\beta$ -hCG 12-14 days following embryo transfer and clinical pregnancy was assessed by ultrasound 2-3 weeks after a positive test.

Frozen embryo transfers (FET) were preferably performed in a natural cycle using hCG trigger. Some FETs

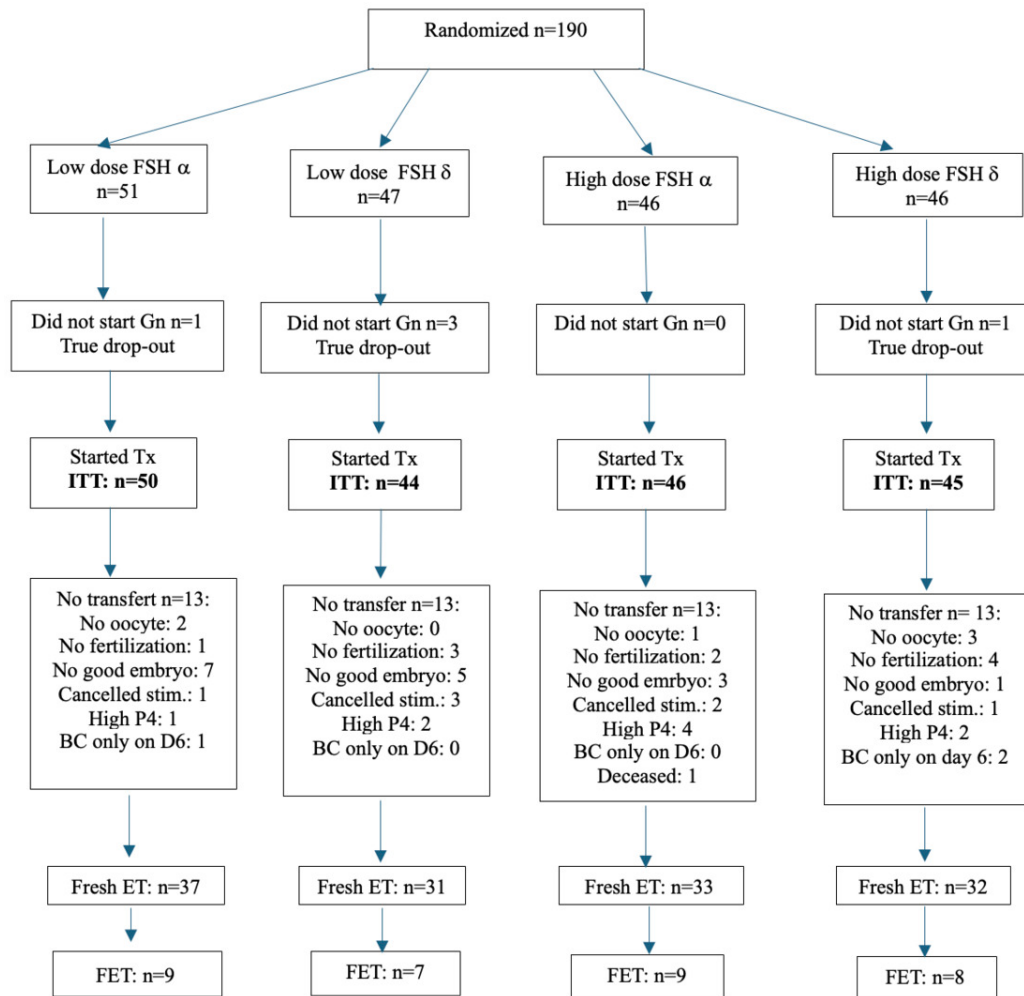
(based on a discussion between the provider and the patient) were carried out in a hormone replacement cycle using oral estradiol (Estrofem Novo Nordisk AS) and vaginal and/or subcutaneous progesterone added when endometrial thickness reached >7 mm.

#### OUTCOME PARAMETERS/ DATA COLLECTION

Data including baseline parameters, stimulation, embryology and clinical outcome parameters were collected in data collections sheets prepared in advance at each site and were then compiled into one final dataset as shown in [Table 2](#). The primary outcome of interest was cCPR. As secondary outcomes, LBR and cLBR with lower vs higher dose and comparison of different follitropins were also studied. CP was defined as an intrauterine sac at 6-8 weeks gestation, LB as the birth of a singleton or twin after 24 weeks of gestation, and cumulative (c) LB as a LB following the fresh or any of the frozen ETs resulting from the same retrieval.

#### STATISTICS

After enrollment of the first 350 patients, an interim analysis was planned to assess sample size assumptions and to test for the effect of gonadotropin dose on outcomes. However, due to various issues including patient death, medication shortages, and insurance requirements, recruitment was stopped, and analysis was performed on 190 enrolled participants, representing 25% of the planned sample size. Post-hoc power analysis revealed that with 190 patients, our study had approximately 15% power to detect the originally anticipated 50% increase in cumulative clinical pregnancy rate and insufficient power (<20%) to detect smaller but clinically meaningful differences of 15-25%. This severe underpowering transformed our study from a definitive efficacy trial to an exploratory analysis.



**Figure 1. Flow of study participants.**

Gn: gonadotropin; FSH: follicle stimulating hormone; Tx: treatment; stim: stimulation; P4: progesterone; BC: blastocyst; ET: embryo transfer; FET: frozen embryo transfer; ITT: intent-to-treat.

Continuous variables were summarized as means  $\pm$  standard deviations (SD), while categorical variables were presented as counts (n) and percentages (%). Data normality was assessed using Shapiro-Wilk tests and QQ-plots. Variables showing significant departure from normality (total gonadotropin dose, stimulation duration, and number of oocytes retrieved) were log-transformed based on Akaike Information Criterion (AIC) model comparison and residual assessment.

For the 2 $\times$ 2 factorial design, we tested main effects of gonadotropin dose (225 IU vs 375 IU daily), FSH type (follicle-stimulating hormone- $\alpha$  vs follicle-stimulating hormone- $\delta$ ), and their interaction. Linear mixed-effects models were employed for continuous outcomes with gonadotropin dose group and FSH type as fixed effects and participating center as a random intercept. Generalized linear mixed-effects models with logit link function were used for binary outcomes using the same fixed and random effects structure. Model assumptions were verified through residual plots and QQ-plots. When model assumptions were violated, non-parametric tests (Wilcoxon rank-sum for continuous variables, Fisher's exact tests for categorical variables) were employed. Missing data were handled using complete case analysis for the primary

analysis, with multiple imputation sensitivity analyses performed for outcomes with >10% missing data. Given the exploratory nature of this severely underpowered study, no adjustment for multiple comparisons was applied, but all p-values should be interpreted as exploratory findings with increased Type I error risk.

Statistical significance was set at  $p < 0.05$ , though emphasis was placed on effect sizes and confidence intervals given the underpowered design. Analysis was performed as both intention-to-treat (including all 190 randomized patients) and as treated (including only the 133 patients who underwent embryo transfer). All analyses were conducted using R statistical software with appropriate packages for mixed-effects modeling and multiple imputation.

## RESULTS

Of the planned 750 enrolled subjects, 190 were randomized (Figure 1). Fresh cycle embryo transfer took place in 133 patients: 68 in the lower dose FSH, while 65 in the higher dose FSH arms. (Figure 1).

This did not represent the interim analysis that was initially planned. Rather, given the number of issues that im-

**Table 2. Baseline, stimulation, embryology and clinical outcome parameters collected during the study.**

| Parameters collected       |                                                      |                                                |                                                                           |
|----------------------------|------------------------------------------------------|------------------------------------------------|---------------------------------------------------------------------------|
| Baseline, demographic      | Stimulation                                          | Embryology                                     | Clinical outcome                                                          |
| Age (years)                | Day-6 E2 level (pmol/l)                              | No of oocytes                                  | Biochemical pregnancy (hCG > 10 IU/l)                                     |
| Cycle day-3 FSH (IU/l)     | E2 and P4 (nmol/l) at last US                        | No of MII oocytes                              | Clinical pregnancy                                                        |
| AMH (ng/ml)                | Number of follicles >10 mm at the end of stimulation | Proportion of MII oocytes (MII/ oocyte number) | Cumulative clinical pregnancy rate                                        |
| AFC                        | Stimulation duration (days)                          | IVF vs ICSI fertilization                      | Live birth rate (pregnancy ending with 1 or more live infants > 24 weeks) |
| Indication for treatment   | Endometrial thickness (mm)                           | No of fertilized (2PN) oocytes                 | Cumulative live birth rate                                                |
| Smoking status (yes vs no) | Gn dose daily/ total (IU)                            | Fertilization rate/ oocyte                     | Week of delivery                                                          |
| BMI (kg/m <sup>2</sup> )   | Trigger mechanism (hCG vs GnRHa)                     | Fertilization rate / MII oocytes               | Birthweight                                                               |
| Cycle number               | Sperm parameters                                     | No of good quality embryos                     | APGAR score                                                               |
|                            |                                                      | No of ET                                       |                                                                           |
|                            |                                                      | No of cryopreserved embryos                    |                                                                           |

FSH: follicle stimulating hormone; AMH: anti-Müllerian hormone; AFC: antral follicle count; BMI: body mass index; E2: estradiol; P4: progesterone; US: ultrasound; Gn: gonadotropin; IU: international unit; No: number; hCG: human chorionic gonadotropin; GnRHa: gonadotropin-releasing hormone agonist; MII: metaphase 2; PN: [pronuclei](#); ET: embryos transferred.

pected recruitment during the study including a death of a patient that was considered unrelated to her treatment (see below); a shortage of GnRH-ant that occurred twice for two months; and the mandated requirement for additional insurance after the estimated study date completion, the joint decision of investigators was to close the study.

#### INTENT-TO-TREAT AND AS TREATED ANALYSIS

Lower and higher dose FSH groups were well-balanced regarding baseline characteristics. ([Table 3](#)). With respect to cycle stimulation characteristics and embryology outcomes, significantly less gonadotropins were used in the lower dose FSH arm (2189 IU vs. 3550 IU,  $p<0.001$ ). ([Table 4](#)) Regarding the ITT analysis, no differences were seen with respect to clinical outcomes (RR CPR: 1.07;0.93-1.23; RR LBR: 1.05;0.94-1.18; RR cCPR: 1.14;0.97-1.34; RR cLBR: 1.04;0.92-1.18) ([Figure 2](#)). In the as treated analysis, while cCPR was significantly higher in the lower dose arm (38.2% vs 23.1%,  $p=0.05$ ), significance was not seen for cLBR (RR CPR: 1.11;0.91-1.35; RR LBR: 1.08;0.92-1.27; RR cCPR: 1.24;0.99-1.56; RR cLBR: 1.08;0.91-1.29). ([Figure 3](#))

#### COMPARISON OF FOLLITROPIN-A AND Δ

When outcomes were compared using different follitropin preparations (FSH- $\alpha$  vs  $\delta$ ), demographic characteristics, cycle stimulation, embryology parameters ([Supplemental Table 1](#)), and clinical outcomes ([Figure 4](#)) were comparable in the four subgroups. Regarding analysis for as treated cycles, while cCPR significantly differed (LD  $\alpha$ : 27.0%, LD  $\delta$ :

51.6%, HD  $\alpha$ : 27.3%, HD  $\delta$ :18.7%,  $p=0.048$ ), this was not noted for cLBR. ([Figure 4, 5](#))

#### ADVERSE EVENTS

One patient died after randomization in the increased dose FSH group while undergoing ovarian stimulation. Her death after the coroner's exam, revealed she suffered from an autoimmune disease that she failed to disclose and flared leading to multiorgan failure and eventually her death that was considered unrelated to her fertility treatment. No other severe adverse events (complications during the retrieval procedure requiring intervention/ hospitalization, ovarian hyperstimulation syndrome or thromboembolic event) were observed during the study.

#### DISCUSSION

Our results do not support superior stimulation, embryology or clinical outcomes when higher dose gonadotropins are used among expected poor responders during IVF. Furthermore, other than cCPR, different follitropin subtypes do not result in improved outcomes.

Induction of multi-follicular development is a critical step of IVF as with each step there is some expected loss progressing from follicle aspiration to embryo implantation.<sup>19</sup> Dose-finding studies of gonadotropins have shown that with higher gonadotropin doses, more follicles are recruited and greater number of oocytes collected<sup>5</sup> but not paralleled by an increase in blastocysts.<sup>2,5</sup> This "contradiction" suggests that the quality of oocytes in a stimulated

**Table 3. Baseline parameters, intent-to treat.**

|                          | Low-dose arm (n=94) | High dose arm (n=91) | p-value |
|--------------------------|---------------------|----------------------|---------|
| Age                      | 36.8 ± 3.3          | 37.1 ± 3.6           | 0.69    |
| AMH (ng/ml)              | 0.7 ± 1.3           | 0.7 ± 0.2            | 0.26    |
| AFC                      | 5.8 ± 2.5           | 6.0 ± 2.5            | 0.93    |
| BMI (kg/m <sup>2</sup> ) | 23.8 ± 4.4          | 24.1 ± 4.1           | 0.56    |
| Cycle number             | 1.8 ± 1.1           | 1.7 ± 1.0            | 0.83    |
| Sperm count (mill/ml)    | 40.6 ± 38.4         | 44.8 ± 40.3          | 0.28    |
| Sperm motility (%)       | 49.8 ± 22.7         | 47.7 ± 23            | 0.86    |

AMH: anti-Müllerian hormone; AFC: antral follicle count; BMI: body mass index.

**Table 4. Stimulation and embryology outcome – intent-to-treat.**

|                                | Low-dose arm (n=94) | High dose arm (n=91) | p-value |
|--------------------------------|---------------------|----------------------|---------|
| E2 on day 6                    | 1781 ± 1319         | 1468 ± 1138          | 0.50    |
| > 10 mm follicles              | 5.7 ± 2.9           | 5.8 ± 2.8            | 0.34    |
| E2 at last US (pmol/l)         | 4094 ± 2122         | 3835 ± 2419          | 0.34    |
| P4 at last US (nmol/l)         | 2.26 ± 1.9          | 2.45 ± 2.28          | 0.36    |
| Length of stimulation          | 10.1 ± 1.9          | 10.0 ± 1.6           | 0.85    |
| EMT (mm)                       | 9.9 ± 2.0           | 10.0 ± 1.64          | 0.68    |
| Total Gn dose (IU)             | 2189 ± 450          | 3550 ± 623           | <0.001  |
| Number of oocytes              | 4.87 ± 2.7          | 4.87 ± 3.2           | 0.99    |
| MII oocytes                    | 3.8 ± 2.4           | 3.6 ± 2.9            | 0.42    |
| Fertilization/ oocyte (%)      | 61.1 ± 29.5         | 62.1 ± 30.1          | 0.78    |
| Fertilization/ MII oocytes (%) | 71.5 ± 30.5         | 71.9 ± 31.3          | 0.88    |
| Good morphology embryos        | 1.7 ± 1.3           | 1.7 ± 1.5            | 0.88    |
| Cryopreserved embryos          | 0.6 ± 1.0           | 0.6 ± 1.1            | 0.81    |

E2: estradiol; P4: progesterone; US: ultrasound; EMT: endometrial thickness; Gn: gonadotropin; IU: international unit; MII: metaphase 2.

cohort is heterogeneous and over certain number of oocytes no further clinical gain can be expected.

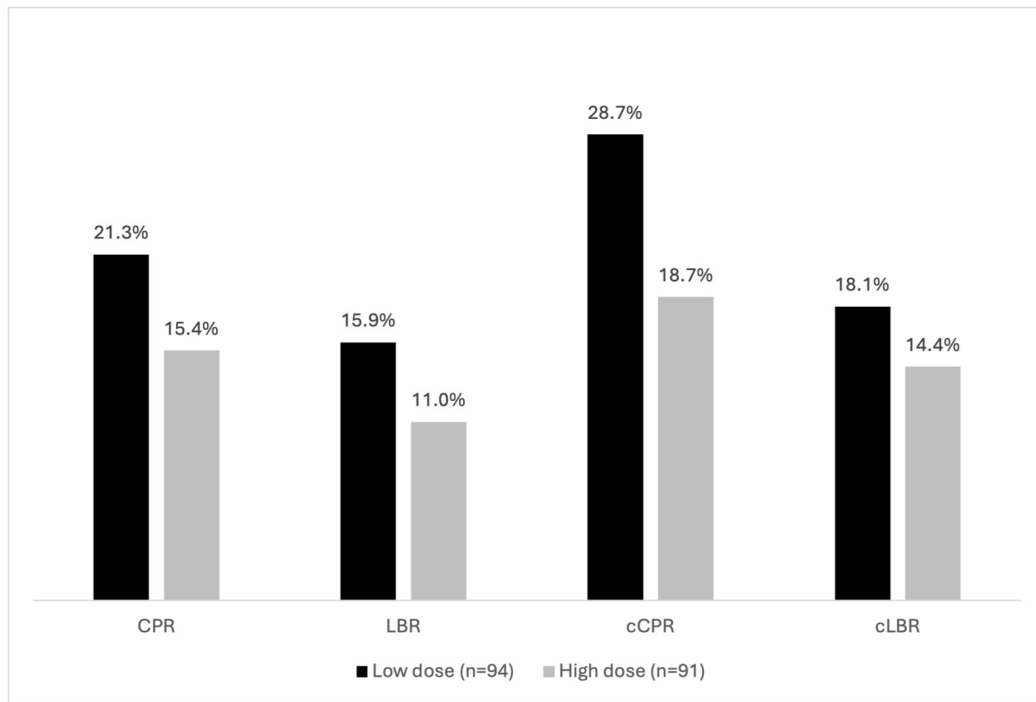
A wide variety of treatment options have been explored in this group of patients<sup>4</sup> including the use of higher doses of gonadotropins.<sup>6–13</sup> Nonetheless, studies are inconsistent including varying stimulation protocols,<sup>6,7,9,12</sup> differing gonadotropin types with dose increases leading to an eventual “high-dose” administration in the low dose arms,<sup>8</sup> and outcome parameters tested have varied (CPR, ongoing PR, LBR) with the most important outcome, cLBR reported only in a small subset of studies.<sup>12,13</sup> Finally, varying criteria to define poor responders<sup>10,12,13</sup> makes it at best difficult to compare the results of the various studies.<sup>14</sup>

Nonetheless, despite these study design differences; studies have overall been “homogenous” including lower cancellation rate<sup>12</sup> and greater retrieved oocytes with higher dosing.<sup>10,12</sup> Moreover, others have suggested an adverse effect of high dose FSH on oocyte/ embryo quality,<sup>20–23</sup> though not a consistent finding.<sup>24–26</sup> Additionally, no differences in clinical outcome, including LBR and cLBR have been demonstrated, resulting in ESHRE COS guideline questioning the benefit of a gonadotropin dose in excess of 150 IU daily and further advising against the use of a dose higher than 300 IU daily.<sup>3</sup>

Nonetheless, given the diagnostic, treatment and reporting inconsistencies of previous studies, we attempted our RCT using the 2016 POSEIDON classification that was introduced to define a more universal identification of poor responders.<sup>16</sup> To avoid previous inconsistencies, we maintained a fixed drug dosing in both the lower and increased dose arms. However, despite this standardized approach, we failed to identify a benefit with either lower or higher dose gonadotropins and FSH formulations.

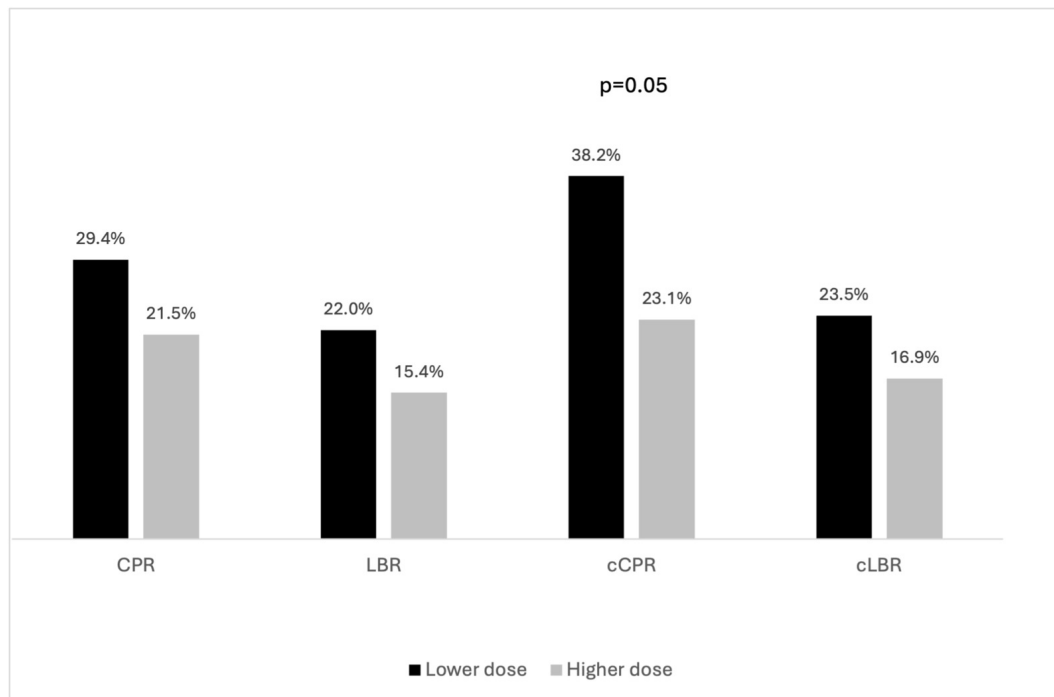
Our study has several strengths. We used standard definitions to identify expected poor responders; patients were randomly assigned to a fixed lower or higher drug dose without dose-adjustment and tested clinically relevant outcomes including cLBR as a measure of the full reproductive potential of the IVF cycle. Further, the multi-center design improves the external validity of the findings though all clinics belong a single health care system following national regulations, and our analysis was performed as an intent-to-treat and as treated.

This study also has several important limitations that significantly affect the interpretation of our findings. The most critical limitation is the severe underpowering resulting from premature study termination, with only 190 participants enrolled (25%) of the planned 750-patient sam-



**Figure 2. Clinical outcome: intent-to-treat.**

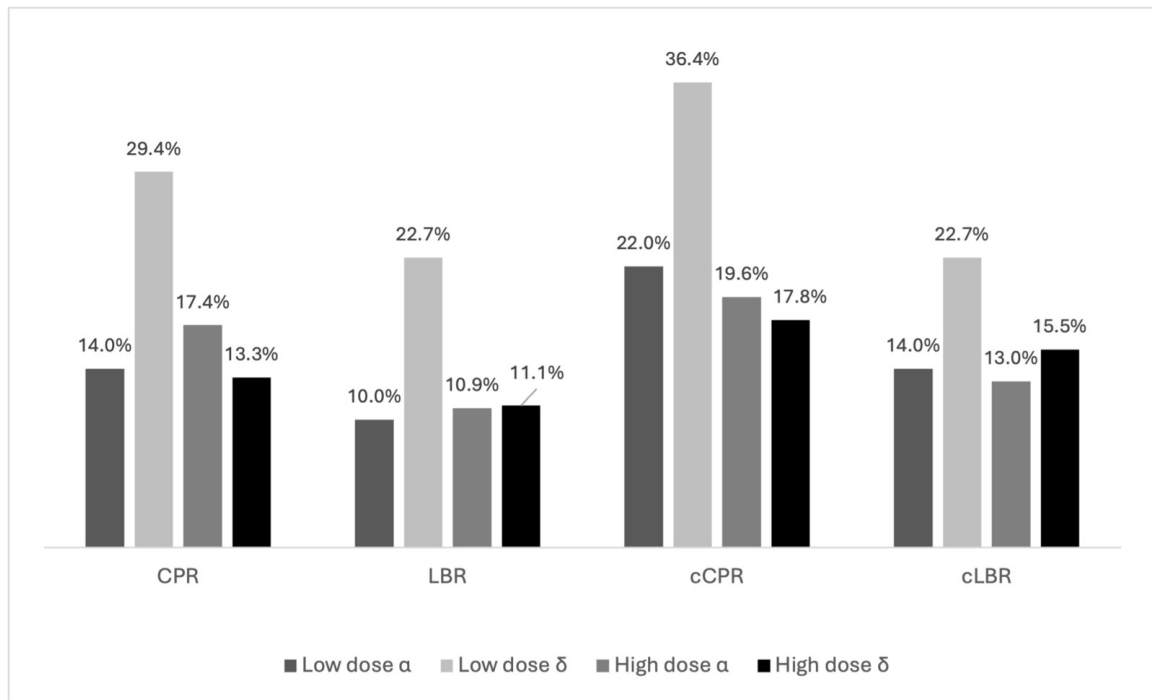
CPR: clinical pregnancy rate; cCPR: cumulative clinical pregnancy rate; LBR: live birth rate; cLBR: cumulative live birth rate. None of the differences are significantly different: CPR:  $p=0.3$ ; cCPR:  $p=0.11$ ; LBR:  $p=0.32$ ; cLBR:  $p=0.48$ .



**Figure 3. Clinical outcome in those cycle in which ET took place (as treated) low versus high dose of gonadotropins. CPR: clinical pregnancy rate; cCPR: cumulative clinical pregnancy rate; LBR: live birth rate; cLBR: cumulative live birth rate.**

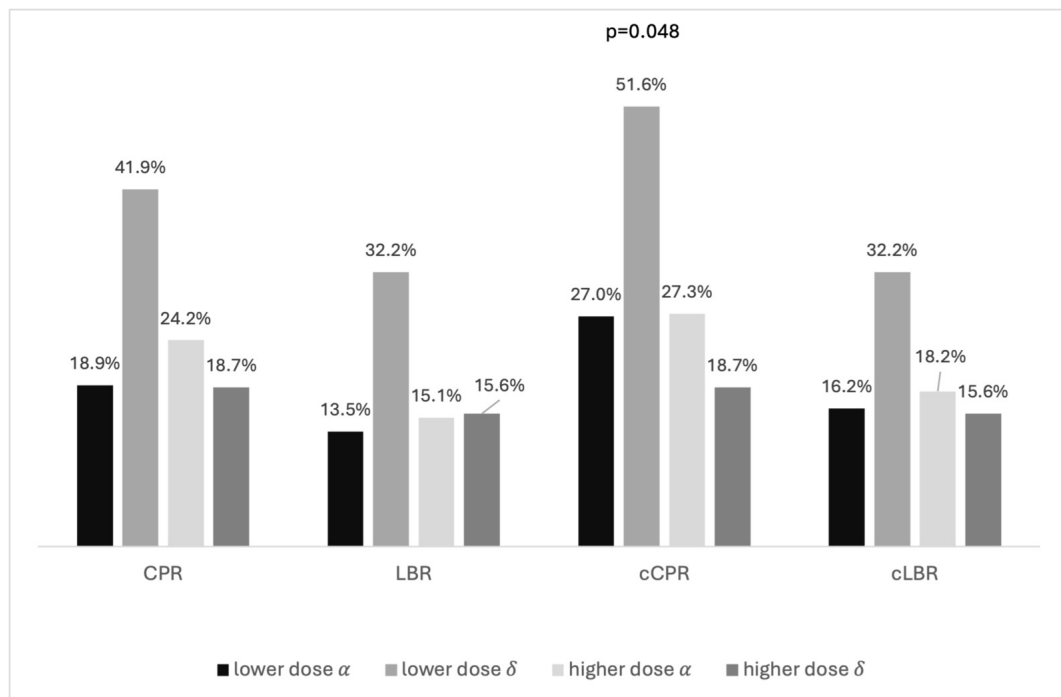
ple size. This dramatic shortfall fundamentally transforms our investigation from a definitive efficacy trial to an exploratory pilot study. For the observed difference in our primary outcome (28.7% vs 18.7% cCPR), approximately 277 participants per group would have been required to

achieve 80% statistical power. This severe underpowering has profound implications for result interpretation. Our negative findings should not be interpreted as definitive evidence that higher gonadotropin doses provide no benefit to poor responders. Rather, they represent insufficient sta-



**Figure 4. Clinical outcome based on lower and higher dose and follitropin type – intent-to-treat.**

CPR: clinical pregnancy rate; cCPR: cumulative clinical pregnancy rate; LBR: live birth rate; cLBR: cumulative live birth rate. None of the differences are significantly different.



**Figure 5. Clinical outcome per embryo transfer (as treated) based on and follitropin type.**

CPR: clinical pregnancy rate; cCPR: cumulative clinical pregnancy rate; LBR: live birth rate; cLBR: cumulative live birth rate.

tistical power to detect potentially clinically meaningful differences, creating substantial risk of Type II error. Thus, while our results are consistent with no benefit from moderate dose escalation and support current evidence-based guidelines, they cannot definitively exclude the possibility

that dose increases provide meaningful clinical improvements.

Several methodological limitations further compromise our findings. The open-label design introduced potential performance and detection bias, as neither patients nor providers were blinded to treatment assignments. This

could have influenced treatment decisions, monitoring intensity, and outcome assessment. The unplanned early termination due to logistical issues (patient death unrelated to treatment, medication shortages, insurance requirements) rather than pre-specified efficacy or futility criteria reduces confidence in our negative results and prevented the planned interim analysis that might have informed sample size adjustments. Our study's generalizability is also limited by several factors. All participating centers were located within a single healthcare system in Hungary, potentially limiting applicability to other healthcare settings with different patient populations, protocols, or resource availability. The exclusion of preimplantation genetic testing and other advanced reproductive technologies due to local regulatory restrictions limits relevance to centers where these techniques are standard practice. Additionally, our definition of "high dose" (375 IU daily) represents a moderate increase compared to doses commonly used in clinical practice (450-600 IU), meaning our findings may not apply to truly high-dose protocols. The study design itself presents limitations. Our sample size calculation was based on potentially unrealistic assumptions, including a 50% relative increase in clinical pregnancy rates with higher dosing and a baseline rate that may have been optimistic for this poor-prognosis population. The 2×2 factorial design, while efficient, may have been underpowered to detect meaningful interactions between gonadotropin dose and FSH formulation. The broad inclusion criteria (BMI 18-35 kg/m<sup>2</sup>) encompassed substantial patient heterogeneity that might have obscured subgroup-specific effects. Data collection and analysis limitations include the lack of standardization of embryo culture conditions and transfer policies across centers, which could have introduced inter-center variability beyond what our statistical models could adequately control. The absence of comprehensive cost-effectiveness analysis, despite mentioning economic implications, limits our ability to provide definitive guidance on the economic aspects of dosing decisions. Furthermore, our follow-up, while adequate for pregnancy outcomes, did not extend to long-term maternal and neonatal health outcomes. Finally, the exclusion of patients with certain baseline characteristics (previous poor response, specific medical conditions) may limit the applicability of our findings to the broader population of poor responders encountered in clinical practice. The restriction to antagonist protocols means our results may not apply to other stimulation approaches commonly used in poor responders. Despite these substantial limitations, our study provides valuable exploratory data suggesting that moderate gonadotropin dose increases (from 225 to 375 IU daily) do not improve clinical outcomes in poor responders, while increasing treatment costs. These findings support current evidence-based guidelines recommending against routine high-dose protocols, though definitive conclusions require confirmation in adequately powered studies.

Although we did not collect data on medication expense, using lower dosing and taking average Hungarian medication and treatment expenses into consideration, the approximately 1400 IU less gonadotropin used in the lower

dose arm resulted in a 15% overall treatment expense reduction.

In conclusion, our findings suggest that a modest dose increase does not improve outcomes, raising questions about the utility of more aggressive dosing protocols. The administration of a more modest dose is likely to be associated with significant cost savings without compromising outcomes though proper cost-effectiveness analysis has to be part of future trials. Given the noted differences in cCPR, studies to assess the impact of newer gonadotropins including follitropin- $\delta$  should be considered in expected poor responder women undergoing IVF. These findings support current evidence-based guidelines recommending against routine high-dose protocols, though definitive conclusions require confirmation in adequately powered studies.

## CLINICAL TRIALS REGISTRATION

NCT05103228 (Oct 21, 2021)

## CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare that could inappropriately influence or bias the work.

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## REFERENCES

1. Polyzos NP, Drakopoulos P, Parra J, Pellicer A, Santos-Ribeiro S, Tournaye H, et al. Cumulative live birth rates according to the number of oocytes retrieved after the first ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection: a multicenter multinational analysis including 15,000 women. *Fertil Steril*. 2018;110(4):661-70.e1.
2. Fanton M, Cho JH, Baker VL, Loewke K. A higher number of oocytes retrieved is associated with an increase in fertilized oocytes, blastocysts, and cumulative live birth rates. *Fertil Steril*. 2023;119(5):762-769. doi:[10.1016/j.fertnstert.2023.01.001](https://doi.org/10.1016/j.fertnstert.2023.01.001)
3. Bosch E, Broer S, Griesinger G, Grynberg M, Humaidan P, Kolibianakis E, et al. ESHRE guideline: ovarian stimulation for IVF/ICSI†. *Hum Reprod Open*. 2020;2:hoaa009.
4. Conforti A, Carbone L, Di Girolamo R, Iorio GG, Guida M, Campitiello MR, et al. Therapeutic management in women with a diminished ovarian reserve: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril*. 2025;123(3):457-476. doi:[10.1016/j.fertnstert.2024.09.038](https://doi.org/10.1016/j.fertnstert.2024.09.038)
5. Arce JC, Andersen AN, Fernández-Sánchez M, Visnova H, Bosch E, García-Velasco JA, et al. Ovarian response to recombinant human follicle-stimulating hormone: a randomized, antimüllerian hormone-stratified, dose-response trial in women undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertil Steril*. 2014;102(6):1633-40.e5. doi:[10.1016/j.fertnstert.2014.08.013](https://doi.org/10.1016/j.fertnstert.2014.08.013)
6. Harrison RF, Jacob S, Spillane H, Mallon E, Hennelly B. A prospective randomized clinical trial of differing starter doses of recombinant follicle-stimulating hormone (follitropin-beta) for first time in vitro fertilization and intracytoplasmic sperm injection treatment cycles. *Fertil Steril*. 2001;75(1):23-31. doi:[10.1016/S0015-0282\(00\)01643-5](https://doi.org/10.1016/S0015-0282(00)01643-5)
7. Berkkanoglu M, Ozgur K. What is the optimum maximal gonadotropin dosage used in microdose flare-up cycles in poor responders? *Fertil Steril*. 2010;94(2):662-665. doi:[10.1016/j.fertnstert.2009.03.027](https://doi.org/10.1016/j.fertnstert.2009.03.027)
8. Klinkert ER, Broekmans FJ, Looman CW, Habbema JD, te Velde ER. Expected poor responders on the basis of an antral follicle count do not benefit from a higher starting dose of gonadotrophins in IVF treatment: a randomized controlled trial. *Hum Reprod*. 2005;20(3):611-615. doi:[10.1093/humrep/deh663](https://doi.org/10.1093/humrep/deh663)
9. Lefebvre J, Antaki R, Kadoch IJ, Dean NL, Sylvestre C, Bissonnette F, et al. 450 IU versus 600 IU gonadotropin for controlled ovarian stimulation in poor responders: a randomized controlled trial. *Fertil Steril*. 2015;104(6):1419-1425. doi:[10.1016/j.fertnstert.2015.08.014](https://doi.org/10.1016/j.fertnstert.2015.08.014)
10. Youssef MA, van Wely M, Al-Inany H, Madani T, Jahangiri N, Khodabakhshi S. A mild ovarian stimulation strategy in women with poor ovarian reserve undergoing IVF: a multicenter randomized non-inferiority trial. *Hum Reprod*. 2017;32(1):112-118.
11. Bastu E, Buyru F, Ozsurmeli M, Demiral I, Dogan M, Yeh J. A randomized, single-blind, prospective trial comparing three different gonadotropin doses with or without addition of letrozole during ovulation stimulation in patients with poor ovarian response. *Eur J Obstet Gynecol Reprod Biol*. 2016;203:30-34. doi:[10.1016/j.ejogrb.2016.05.027](https://doi.org/10.1016/j.ejogrb.2016.05.027)
12. van Tilborg TC, Torrance HL, Oudshoorn SC, Eijkemans MJC, Koks CAM, Verhoeve HR, et al. Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 1: The predicted poor responder. *Hum Reprod*. 2017;32(12):2496-2505.
13. Liu X, Li T, Wang B, Xiao X, Liang X, Huang R. Mild stimulation protocol vs conventional controlled ovarian stimulation protocol in poor ovarian response patients: a prospective randomized controlled trial. *Arch Gynecol Obstet*. 2020;301(5):1331-1339. doi:[10.1007/s00404-020-05513-6](https://doi.org/10.1007/s00404-020-05513-6)
14. Polyzos NP, Devroey P. A systematic review of randomized trials for the treatment of poor ovarian responders: is there any light at the end of the tunnel? *Fertil Steril*. 2011;96(5):1058-61.e7. doi:[10.1016/j.fertnstert.2011.09.048](https://doi.org/10.1016/j.fertnstert.2011.09.048)
15. Ferraretti AP, La Marca A, Fauser BC, et al. ESHRE consensus on the definition of “poor response” to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Hum Reprod*. 2011;26(7):1616-1624. doi:[10.1093/humrep/der092](https://doi.org/10.1093/humrep/der092)

16. Alviggi C, Andersen CY, Buehler K, Conforti A, De Placido G, Esteves SC, et al. A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept. *Fertil Steril*. 2016;105(6):1452-1453. doi:[10.1016/j.fertnstert.2016.02.005](https://doi.org/10.1016/j.fertnstert.2016.02.005)
17. Arce JC, Larsson P, García-Velasco JA. Establishing the follitropin delta dose that provides a comparable ovarian response to 150 IU/day follitropin alfa. *Reprod Biomed Online*. 2020;41(4):616-622. doi:[10.1016/j.rbmo.2020.07.006](https://doi.org/10.1016/j.rbmo.2020.07.006)
18. Nyboe Andersen A, Nelson SM, Fauser BC, García-Velasco JA, Klein BM, Arce JC. Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicenter, randomized, controlled, assessor-blinded, phase 3 noninferiority trial. *Fertil Steril*. 2017;107(2):387-396.e4.
19. Vlasisavljevic V, Apter S, Capalbo A, D'Angelo A, Gianaroli L, Griesinger G, et al. The Maribor consensus: report of an expert meeting on the development of performance indicators for clinical practice in ART. *Hum Reprod Open*. 2021;3:hoab022.
20. Baart EB, Martini E, Eijkemans MJ, Van Opstal D, Beckers NG, Verhoeff A, et al. Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial. *Hum Reprod*. 2007;22(4):980-988. doi:[10.1093/humrep/del484](https://doi.org/10.1093/humrep/del484)
21. Rubio C, Mercader A, Alamá P, Lizán C, Rodrigo L, Labarta E, et al. Prospective cohort study in high responder oocyte donors using two hormonal stimulation protocols: impact on embryo aneuploidy and development. *Hum Reprod*. 2010;25(9):2290-2297. doi:[10.1093/humrep/deq174](https://doi.org/10.1093/humrep/deq174)
22. Bernstein LR, Mackenzie ACL, Durkin K, Kraemer DC, Chaffin CL, Merchenthaler I. Maternal age and gonadotrophin elevation cooperatively decrease viable ovulated oocytes and increase ootoxicity, chromosome-, and spindle-misalignments: "2-Hit" and "FSH-OoToxicity" mechanisms as new reproductive aging hypotheses. *Mol Hum Reprod*. 2023;29(10):gaad030. doi:[10.1093/molehr/gaad030](https://doi.org/10.1093/molehr/gaad030)
23. Baker VL, Brown MB, Luke B, Smith GW, Ireland JJ. Gonadotropin dose is negatively correlated with live birth rate: analysis of more than 650,000 assisted reproductive technology cycles. *Fertil Steril*. 2015;104(5):1145-1152. doi:[10.1016/j.fertnstert.2015.07.1151](https://doi.org/10.1016/j.fertnstert.2015.07.1151). PMID:26297646
24. Irani M, Canon C, Robles A, Maddy B, Gunnala V, Qin X, et al. No effect of ovarian stimulation and oocyte yield on euploidy and live birth rates: an analysis of 12 298 trophoctoderm biopsies. *Hum Reprod*. 2020;35(5):1082-1089. doi:[10.1093/humrep/deaa028](https://doi.org/10.1093/humrep/deaa028)
25. Sekhon L, Shaia K, Santistevan A, Cohn KH, Lee JA, Beim PY, et al. The cumulative dose of gonadotropins used for controlled ovarian stimulation does not influence the odds of embryonic aneuploidy in patients with normal ovarian response. *J Assist Reprod Genet*. 2017;34(6):749-758. doi:[10.1007/s10815-017-0909-3](https://doi.org/10.1007/s10815-017-0909-3). PMID:28321529
26. Wu Q, Li H, Zhu Y, Jiang W, Lu J, Wei D, et al. Dosage of exogenous gonadotropins is not associated with blastocyst aneuploidy or live-birth rates in PGS cycles in Chinese women. *Hum Reprod*. 2018;33(10):1875-1882. doi:[10.1093/humrep/dey270](https://doi.org/10.1093/humrep/dey270)

**Supplemental Table 1. Baseline, stimulation, and embryology parameters based on follitropin type.**

|                                | Low dose $\alpha$<br>(n=50) | Low dose $\delta$<br>(n=44) | High dose $\alpha$<br>(n=46) | High dose $\delta$<br>(n=45) | p-value |
|--------------------------------|-----------------------------|-----------------------------|------------------------------|------------------------------|---------|
| Age (yrs)                      | 36.3 $\pm$ 3.5              | 37.5 $\pm$ 2.9              | 37.3 $\pm$ 3.7               | 36.9 $\pm$ 3.5               | 0.12    |
| AMH (ng/ml)                    | 0.7 $\pm$ 0.3               | 0.7 $\pm$ 0.2               | 0.7 $\pm$ 0.2                | 0.7 $\pm$ 0.2                | 0.67    |
| BMI (kg/m <sup>2</sup> )       | 24.0 $\pm$ 4.6              | 23.4 $\pm$ 4.3              | 24.0 $\pm$ 4.2               | 24.1 $\pm$ 4.1               | 0.56    |
| Cycle number                   | 1.7 $\pm$ 1.1               | 1.9 $\pm$ 1.1               | 1.4 $\pm$ 0.7                | 2.1 $\pm$ 1.1                | 0.20    |
| Sperm count (mill/ml)          | 38.4 $\pm$ 29.6             | 43.1 $\pm$ 47.0             | 41.7 $\pm$ 42.2              | 47.8 $\pm$ 38.5              | 0.73    |
| Sperm motility (%)             | 51.7 $\pm$ 23.1             | 47.6 $\pm$ 22.4             | 43.8 $\pm$ 22.0              | 51.5 $\pm$ 23.5              | 0.28    |
| >10 mm follicles               | 6.1 $\pm$ 3.3               | 5.3 $\pm$ 2.4               | 5.9 $\pm$ 2.7                | 5.7 $\pm$ 2.8                | 0.35    |
| E2 at last US                  | 4016 $\pm$ 2300             | 4183 $\pm$ 1928             | 3999 $\pm$ 2565              | 3672 $\pm$ 2284              | 0.40    |
| P4 at last US                  | 1.9 $\pm$ 1.1               | 2.6 $\pm$ 2.6               | 2.5 $\pm$ 2.7                | 2.4 $\pm$ 1.9                | 0.85    |
| Length of stimulation          | 10.0 $\pm$ 2.3              | 10.1 $\pm$ 1.3              | 9.9 $\pm$ 1.7                | 10.1 $\pm$ 1.6               | 0.88    |
| EMT (mm)                       | 9.8 $\pm$ 2.5               | 10.1 $\pm$ 1.3              | 10.2 $\pm$ 2.6               | 9.8 $\pm$ 1.5                | 0.18    |
| Total Gn dose (IU)             | 2192 $\pm$ 523              | 2185 $\pm$ 352              | 3484 $\pm$ 597               | 3618 $\pm$ 650               | 0.52    |
| Number of oocytes              | 4.9 $\pm$ 2.8               | 4.8 $\pm$ 2.5               | 5.2 $\pm$ 3.5                | 4.5 $\pm$ 2.8                | 0.28    |
| MII oocytes                    | 3.9 $\pm$ 2.7               | 3.7 $\pm$ 2.2               | 4.1 $\pm$ 3.1                | 3.1 $\pm$ 2.6                | 0.17    |
| Fertilization/ oocyte (%)      | 60.8 $\pm$ 28.5             | 61.6 $\pm$ 31.0             | 63.1 $\pm$ 27.3              | 61.0 $\pm$ 33.0              | 0.78    |
| Fertilization/ MII oocytes (%) | 73.2 $\pm$ 29.6             | 69.7 $\pm$ 31.8             | 75.9 $\pm$ 26.2              | 68.0 $\pm$ 35.4              | 0.30    |
| Number of embryos              | 2.8 $\pm$ 1.9               | 3.0 $\pm$ 1.8               | 3.1 $\pm$ 1.9                | 3.0 $\pm$ 1.8                | 0.39    |
| Good morphology embryos        | 1.6 $\pm$ 1.4               | 1.7 $\pm$ 1.3               | 1.8 $\pm$ 1.8                | 1.6 $\pm$ 1.2                | 0.66    |
| Number of ET                   | 1.3 $\pm$ 0.5               | 1.5 $\pm$ 0.6               | 1.5 $\pm$ 0.6                | 1.6 $\pm$ 0.5                | 0.84    |
| Cryopreserved embryos          | 0.5 $\pm$ 0.8               | 0.7 $\pm$ 1.1               | 0.6 $\pm$ 1.0                | 0.5 $\pm$ 1.1                | 0.35    |

AMH: anti-Müllerian hormone; BMI: body mass index; E2: estradiol; P4: progesterone; US: ultrasound; EMT: endometrial thickness; Gn: gonadotropin; IU: international unit; MII: metaphase 2; ET: embryos transferred.