# Predictors of Gonadotropin Efficiency Index (GEI): a regression-based model using patient and stimulation parameters in controlled ovarian stimulation cycles

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## Abstract

***Objectives.*** *In assisted reproductive technology (ART), optimizing gonadotropin usage is critical for both clinical efficacy and cost-efficiency. The Gonadotropin Efficiency Index (GEI), defined as the total gonadotropin dose per grade A embryo (IU/G1), offers a novel metric to quantify stimulation efficiency. However, predictors of GEI have not been well-characterized. Our aim was to identify patient and stimulation-related parameters that significantly predict gonadotropin efficiency using a multivariate regression model.* ***Materials and method.*** *This retrospective cohort study analyzed 300 patients undergoing controlled ovarian stimulation using either recombinant FSH (rFSH) or human menopausal gonadotropin (hMG). Baseline variables (age, BMI, AFC, hormonal profile), protocol details and outcomes (total dose, number of embryos, grade A embryos) were collected. GEI was calculated as IU/grade A embryo. Linear regression was performed to identify independent predictors of GEI.* ***Results.*** *The mean GEI was significantly lower in the rFSH group ($p<0.001$). AFC ($\beta = -0.45$; $p<0.001$) and age ($\beta=0.36$; $p=0.002$) were significant predictors of higher GEI. The use of hMG, lower AFC and advanced age were independently associated with poorer gonadotropin efficiency. A multivariate model predicted GEI with $R^2=0.42$.* ***Conclusions.*** *Antral follicle count and patient age are significant predictors of gonadotropin efficiency. Predictive modeling of GEI may offer individualized stimulation planning, minimizing drug usage and optimizing outcomes in ART cycles.*

***Keywords:*** *gonadotropin efficiency index, controlled ovarian stimulation, embryo quality, regression model*

## Rezumat

***Obiectiv.*** *În tehnicile de reproducere umană asistată (ART), optimizarea utilizării gonadotropinelor este esențială atât pentru eficacitatea clinică, cât și pentru cost-eficienţă. Indicele de Eficiență a Gonadotropinelor (GEI), definit ca doza totală de gonadotropine per embrion de grad A (UI/G1), oferă un nou indicator pentru cuantificarea eficienței stimulării. Totuși, predictorii GEI nu au fost caracterizați în mod adecvat. Scopul acestui studiu a fost de a identifica parametrii pacientului și ai stimulării care prezic în mod semnificativ eficiența gonadotropinelor, folosind un model de regresie multivariată.* ***Materiale și metodă.*** *Acest studiu retrospectiv de cohortă a analizat 300 de paciente supuse stimulării ovariene controlate, utilizând fie FSH recombinant (rFSH), fie gonadotropină umană de menopauză (hMG). Au fost colectate variabilele de bază (vârsta, IMC, AFC, profil hormonal), detaliile protocolului și rezultatele (doza totală, numărul de embrioni, embrioni de grad A). GEI a fost calculat ca UI/embrion de grad A. Am efectuat regresie liniară pentru identificarea predictorilor independenți ai GEI.* ***Rezultate.*** *GEI mediu a fost semnificativ mai mic în grupul rFSH ($p<0,001$). AFC ($\beta = -0,45$; $p<0,001$) și vârsta ($\beta=0,36$; $p=0,002$) au fost predictori semnificativi ai unui GEI mai mare. Utilizarea hMG, un AFC mai redus și vârsta avansată au fost asociate independent cu o eficiență mai scăzută a gonadotropinelor. Modelul multivariat a prezis GEI cu $R^2=0,42$.* ***Concluzii.*** *Numărul de foliculi antrali și vârsta pacientei sunt predictori semnificativi ai eficienței gonadotropinelor. Un model predictiv al GEI poate oferi o planificare individualizată a stimulării, reducând utilizarea medicamentelor și optimizând rezultatele în ciclurile de ART.*

***Cuvinte-cheie:*** *indice de eficiență a gonadotropinelor, stimulare ovariană controlată, calitatea embrionilor, model de regresie*

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*Predictori ai Indicelui de Eficiență a Gonadotropinelor (GEI): un model bazat pe regresie, folosind parametrii pacientei și ai stimulării în ciclurile de stimulare ovariană controlată*

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## Introduction

Controlled ovarian stimulation (COS) is a cornerstone of assisted reproductive technology (ART), aiming to recruit multiple follicles and maximize the number of oocytes retrieved for *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI)[1]. Over the years, the evolution of stimulation protocols and gonadotropin preparations has allowed clinicians to tailor treatment based on ovarian reserve and response profiles[2]. However, despite these advances, one of the persisting challenges in ART is optimizing the biological and economic efficiency of stimulation regimens across diverse patient populations[3]. Traditionally, the success of stimulation has been gauged by the number of oocytes retrieved or the total number of embryos formed[4]. However, these metrics often fail to account for embryo quality, which is a more direct determinant of implantation potential and live birth outcomes[5]. Moreover, they do not consider the amount of gonadotropins required to achieve these outcomes, overlooking the economic and clinical burden of higher doses, especially in resource-constrained settings[6]. The development of the Gonadotropin Efficiency Index (GEI) – defined as the total International Units (IU) of gonadotropins administered per Grade A embryo produced – offers a novel and clinically meaningful performance indicator. This metric integrates both quality and quantity of stimulation outcomes, providing a refined measure of stimulation efficiency. A lower GEI indicates that fewer gonadotropin units were needed to yield top-quality embryos, which may translate into reduced cost, lower patient burden and improved clinical outcomes[7]. Recombinant FSH (rFSH) and human menopausal gonadotropin (hMG) remain the most commonly used gonadotropins in controlled ovarian stimulation. While multiple studies have compared their effects on oocyte yield and pregnancy outcomes[8,9], few have adjusted for quality-adjusted embryo yield or stimulation efficiency. Furthermore, there is a lack of predictive modeling in the literature that helps identify patient-level or protocol-related factors influencing gonadotropin efficiency[10]. The ability to predict GEI prior to starting stimulation could offer valuable insight into selecting the optimal protocol for an individual patient, thus promoting personalized, outcome-driven reproductive care[11]. Against this backdrop, the present study was conducted to explore the determinants of GEI using real-world retrospective data. By incorporating baseline patient characteristics (such as age, BMI and ovarian reserve markers) along with stimulation parameters (gonadotropin type, total dose, duration), we aimed to develop a predictive model for Gonadotropin Efficiency Index. Such a model could serve as a practical clinical tool to guide COS planning, particularly in settings where cost-effectiveness and embryo quality are equally prioritized[12].

## Materials and method

### Study design and setting

This was a retrospective, observational study conducted at a tertiary-care fertility center over the period between January 2022 and June 2023. The study was approved by the institutional ethics committee. A total of 300 women who underwent *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycles using either recombinant FSH (rFSH) or human menopausal gonadotropin (hMG) were included.

### Inclusion and exclusion criteria

Women aged between 22 and 40 years old, undergoing fresh IVF/ICSI cycles, were included. Only those with a documented antral follicle count (AFC) and baseline hormone profile (day 2 FSH, LH, estradiol) were considered. Patients with donor oocytes, uterine anomalies, recurrent implantation failure, endometriosis stage III-IV, or medical comorbidities affecting ovarian response (e.g., PCOS, thyroid dysfunction) were excluded.

### Study groups and matching

Patients were divided into two groups, based on the type of gonadotropin used for stimulation:

- **Group A (rFSH)** – 150 patients stimulated with recombinant FSH.
- **Group B (hMG)** – 150 patients stimulated with human menopausal gonadotropin.

To minimize confounding, the patients were matched 1:1 based on age, AFC, Body Mass Index (BMI) and baseline FSH levels.

### Controlled ovarian stimulation protocol

All patients underwent controlled ovarian stimulation using either an antagonist protocol or long GnRH agonist protocol, depending on clinician discretion and patient characteristics. Ovarian response was monitored *via* serial transvaginal ultrasound and serum estradiol levels. Ovulation was triggered using recombinant hCG or dual trigger when appropriate, and oocyte retrieval was performed 35-36 hours later.

### Embryological assessment

Retrieved oocytes were inseminated *via* IVF or ICSI depending on semen parameters. Embryos were evaluated on day 3 and/or day 5, using standard morphological criteria. Grade A embryos were defined based on blastomere symmetry, fragmentation score and absence of multinucleation (day 3), or expansion, inner cell mass (ICM) and trophectoderm grading (day 5). Embryo quality assessment was blinded to gonadotropin type.

### Calculation of Gonadotropin Efficiency Index

The Gonadotropin Efficiency Index (GEI) was defined as:

GEI = Total gonadotropin dose used (IU) ÷ Number of Grade A embryos formed.

Lower GEI values represented greater stimulation efficiency.

### Data collection and variables

The following variables were extracted:

- **Demographic** – age, BMI.
- **Ovarian reserve** – AFC, day 2 FSH.
- **Stimulation parameters** – gonadotropin type, total dose (IU), duration (days), protocol type.
- **Outcomes** – number of oocytes retrieved, mature oocytes (MII), total embryos, Grade A embryos, GEI.

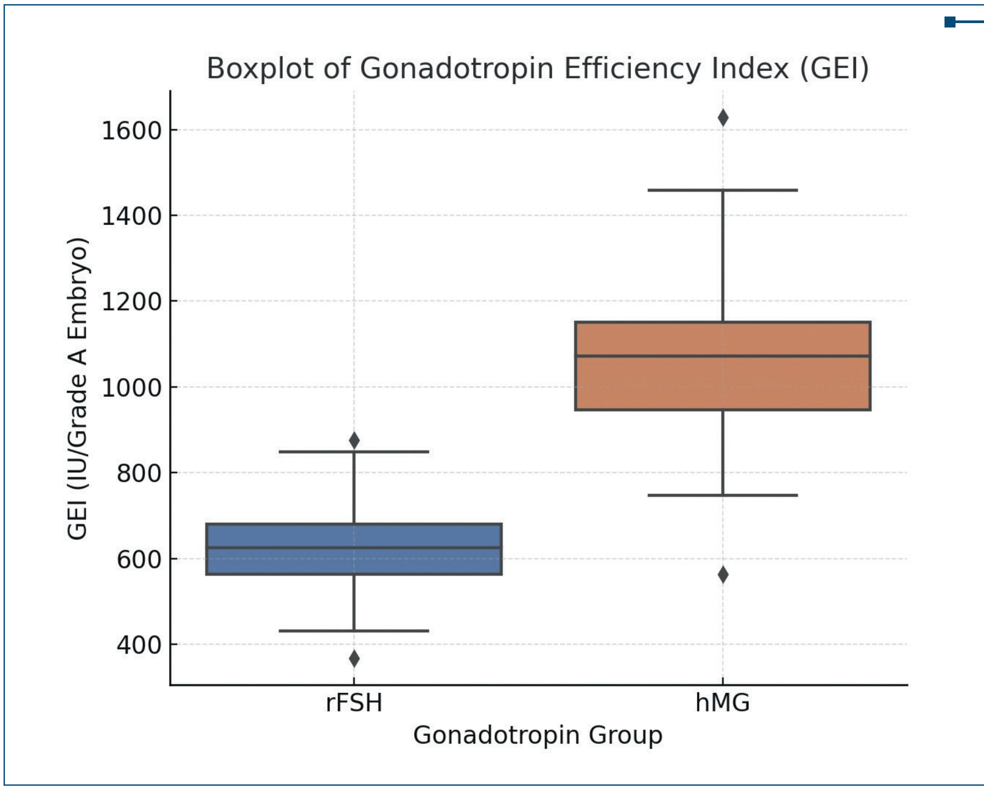


***Figure 1.** A boxplot comparing GEI values between groups demonstrated significantly lower GEI in the rFSH group (p<0.001)*

**Statistical analysis**

Descriptive statistics were reported as mean ± standard deviation for continuous variables and percentages for categorical data. Group comparisons (rFSH versus hMG) were performed using Student's t-test or Mann-Whitney U test for continuous variables and Chi-square test for categorical variables. To identify independent predictors of GEI, a multivariate linear regression model was constructed using GEI as the dependent variable. Covariates included age, BMI, AFC, gonadotropin type, total IU and stimulation duration. Model diagnostics ($R^2$, variance inflation factor [VIF]) were assessed to confirm model validity.

Statistical significance was set at p<0.05. Analyses were performed using SPSS version 2.0.

## Results

**Baseline characteristics**

A total of 300 patients were included, divided equally into two stimulation groups: 150 patients received recombinant FSH (rFSH), and 150 patients received human menopausal gonadotropin (hMG). The groups were matched for age, BMI, antral follicle count (AFC) and baseline day 2 FSH levels. Table 1 summarizes the baseline characteristics.

**Stimulation outcomes and embryo quality**

The mean total gonadotropin dose was significantly higher in the hMG group. The rFSH group yielded more Grade A embryos and had a lower Gonadotropin Efficiency Index.

**Regression analysis**

To identify independent predictors of gonadotropin efficiency, a multivariate linear regression model was built using GEI as the dependent variable. Independent variables included: age, BMI, AFC, gonadotropin type, total stimulation dose and stimulation duration.

The final model accounted for **42% of the variance in GEI** (adjusted $R^2$=0.42). Age, AFC and gonadotropin type were the strongest predictors of efficiency.

## Discussion

In assisted reproductive technology (ART), maximizing the quality and quantity of embryos while minimizing cost and medication burden is an evolving priority. This study introduces the Gonadotropin Efficiency Index (GEI) – defined as the total IU of gonadotropins administered per Grade A embryo – as a novel, biologically relevant and cost-adjusted metric to evaluate the effectiveness of controlled ovarian stimulation (COS). To our knowledge, this is one of the first studies to quantitatively assess predictors of GEI and construct a regression-based model to guide individualized COS planning. Our findings indicate that antral follicle count (AFC) and patient age are significant, independent predictors of GEI. AFC demonstrated a strong inverse correlation with GEI, supporting its established role as a robust marker of ovarian reserve and predictor of ovarian responsiveness[1-3]. Women with higher AFC required fewer gonadotropins per high-quality embryo, suggesting more efficient follicular recruitment and oocyte maturation. This aligns with previous work

**Table 1** Baseline characteristics of the study population

| Parameter | rFSH Group (n=150) | hMG Group (n=150) | p-value |
|---|---|---|---|
| **Age (years)** | 31.2 ± 3.6 | 31.5 ± 3.9 | 0.48 |
| **BMI (kg/m$^2$)** | 24.7 ± 2.9 | 24.9 ± 3.1 | 0.66 |
| **AFC** | 10.2 ± 2.4 | 10.1 ± 2.7 | 0.74 |
| **Day 2 FSH (IU/L)** | 6.5 ± 1.3 | 6.6 ± 1.5 | 0.57 |

*(Values shown as mean ± SD)*

**Table 2** Stimulation and embryo outcomes

| Outcome | rFSH Group | hMG Group | p-value |
|---|---|---|---|
| Total gonadotropin dose (IU) | 2032 ± 342 | 2540 ± 410 | <0.001 |
| Number of oocytes retrieved | 10.4 ± 3.2 | 9.1 ± 3 | 0.002 |
| Grade A embryos | 3.2 ± 1.6 | 2.4 ± 1.4 | <0.001 |
| **GEI (IU/Grade A embryo)** | **634 ± 178** | **1058 ± 245** | **<0.001** |

**Table 3** Multivariate regression model predicting GEI

| Predictor | β coefficient | Standard error | p-value |
|---|---|---|---|
| Age (years) | +16.3 | 5.4 | 0.003 |
| AFC | –21.8 | 6.2 | <0.001 |
| Gonadotropin type (rFSH=0, hMG=1) | +188.5 | 31.2 | <0.001 |
| BMI | +4.2 | 3.1 | 0.18 |
| Total dose (IU) | Not retained | – | – |

indicating that AFC not only correlates with oocyte yield, but may also indirectly reflect granulosa cell environment and follicular synchrony[4]. Similarly, advanced maternal age was associated with significantly higher GEI. This likely reflects the well-established age-related decline in oocyte competence, mitochondrial dysfunction and chromosomal segregation errors – all of which negatively impact embryo quality[5-7]. Age is a non-modifiable but critical factor in ART, and our findings support its integration into predictive models to anticipate stimulation outcomes and guide treatment decisions. Interestingly, BMI did not significantly impact GEI in our model, though literature remains mixed on this association. Some studies suggest higher BMI impairs ovarian response due to altered steroidogenesis, insulin resistance, or altered pharmacokinetics of gonadotropins[8-10]. The lack of significance in our cohort may be attributed to the relatively narrow BMI range and careful dose adjustment practices in our unit. A key observation in this study was that patients receiving recombinant FSH (rFSH) had significantly lower GEI compared to those receiving human menopausal gonadotropin (hMG). This implies greater stimulation efficiency per IU with rFSH, likely due to its higher purity, more consistent bioactivity and targeted receptor affinity[11-13]. While previous randomized controlled trials have shown similar pregnancy outcomes between rFSH and hMG, those studies often focus on live birth or total oocytes, without evaluating embryo quality-adjusted

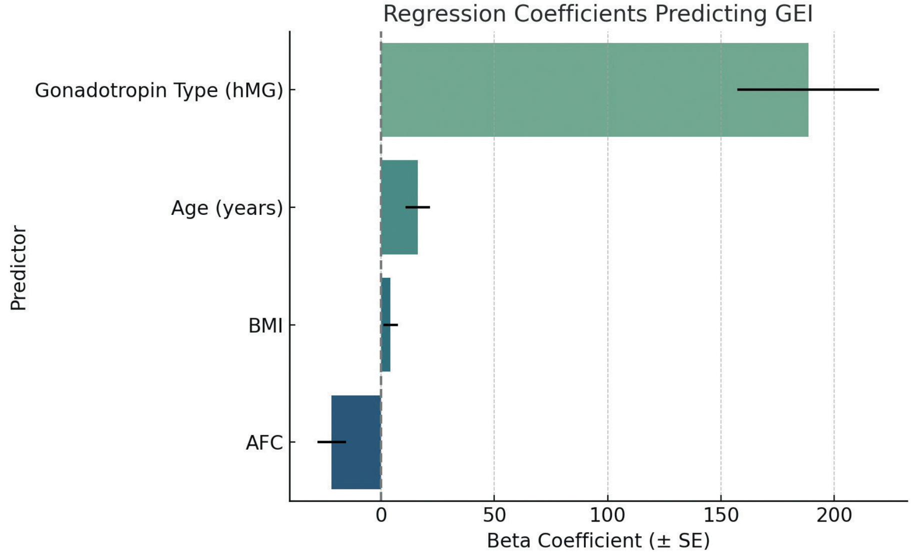


***Figure 2.*** *A regression coefficient plot illustrated the inverse relationship between AFC and GEI, and the strong impact of gonadotropin type on efficiency*

cost efficiency[14-16]. Our use of GEI fills this knowledge gap by incorporating embryo grade, which directly influences implantation potential and clinical success. The multivariate regression model we developed explained approximately 42% of the variability in GEI. Although COS outcomes are inherently multifactorial and influenced by embryology lab standards, genetics and endometrial receptivity, the model's predictive capability is clinically meaningful. With variables such as age, AFC and gonadotropin type, clinicians can estimate a patient's expected efficiency profile before initiating stimulation – thereby individualizing gonadotropin dosing or protocol selection. This approach aligns with the broader movement toward personalized medicine in reproductive care[17,18]. Additionally, the simplicity of the GEI metric allows for easy integration into clinical dashboards, EMR-based calculators, or IVF simulation software. In high-volume ART centers or resource-constrained settings, cost-effective embryo yield is as important as absolute success rates, particularly in self-funded treatment cycles. Tools that combine clinical prediction with cost utility have the potential to improve not only patient satisfaction but also clinic resource optimization. However, this study is not without limitations. Its retrospective design inherently limits causal inference, although robust matching and statistical control for confounders were performed. Furthermore, embryo grading, while standardized and performed by experienced embryologists, remains subjective and may differ across centers. Another limitation is that GEI reflects efficiency up to embryo formation, but does not account for downstream outcomes such as implantation, pregnancy, or live birth. Hence, while GEI is a powerful early-stage metric, it should eventually be linked with cumulative pregnancy outcomes in future studies. Lastly, our study was conducted in a single tertiary-care IVF center which, although it enhances uniformity of protocols and lab conditions, may limit generalizability to other geographic or demographic populations.

## Conclusions

The Gonadotropin Efficiency Index (GEI), defined as the ratio of total gonadotropin dose to the number of Grade A embryos, is a clinically meaningful metric that integrates both cost and embryo quality in evaluating ovarian stimulation. In this study, GEI was significantly influenced by patient age, ovarian reserve (AFC) and the type of gonadotropin used, with recombinant FSH demonstrating superior stimulation efficiency compared to hMG. The development of a predictive model using baseline parameters allows for individualized planning of stimulation protocols, with the potential to improve treatment cost-effectiveness and optimize embryo quality. Incorporating the Gonadotropin Efficiency Index into routine assessment can enhance clinical decision-making, especially in settings where both biological outcomes and affordability are critical considerations. Future prospective and multicentric studies are warranted to validate GEI against long-term outcomes such as cumulative pregnancy rates and to explore its integration with other individualized ART strategies. ■

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