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Unexpected hypo-responders in in vitro fertilization: The impact of higher gonadotropin doses on oocyte yield

Tüp bebekte beklenmedik düşük yanıt veren grupta: Daha yüksek gonadotropin dozlarının oosit verimine etkisi

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Abstract

Objective: This study assessed the impact of increased initial gonadotropin doses on ovarian stimulation (OS) outcomes in unexpected hypo-responders [Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) 1-2 group] with suboptimal mature oocyte yield, despite normal ovarian reserve markers, during their first OS cycle.

Materials and Methods: Conducted at a referral infertility clinic, this observational study included women who retrieved fewer than nine oocytes during their first OS cycle despite gonadotropin doses of 150-225 international unit (IU)/day starting from cycle day two. Women who underwent a second OS cycle following unsuccessful conception were included. Gonadotropin doses were increased to 225 or 300 IU recombinant follicle-stimulating hormone (FSH) (recFSH) based on body mass index. Each patient served as her own control, with first and second OS cycles compared in terms of oocyte yield, follicular output ratio (FORT), and follicle-to-oocyte index (FOI).

Results: Among 289 unexpected hypo-responders (12% prevalence), the mean age was 34.2 years, and the mean anti-müllerian hormone level was 3.4 ng/mL. The stimulation duration was similar between cycles (11.2 days). The second OS cycle showed significant improvements in total oocytes, metaphase II oocytes, FORT, FOI, cleavage-stage embryos, and blastocysts ($p<0.05$).

Conclusion: Increasing gonadotropin doses in subsequent cycles improves oocyte yield and embryological outcomes in unexpected hypo-responders (POSEIDON 1-2) with normal ovarian reserve markers.

Keywords: Infertility, ovulation induction, *in vitro* oocyte maturation techniques

Öz

Amaç: Gonadotropin başlangıç dozlarının artırılması, normal over rezervi belirteçlerine rağmen suboptimal yanıt gösteren beklenmedik düşük yanıtlayıcılar [Bireyselleştirilmiş Oosit Sayısını Kapsayan Hasta Odaklı Stratejiler (POSEIDON) 1-2] için oosit verimini ve embriyolojik sonuçları iyileştirir. Bu çalışma, ilk over stimülasyon (OS) sikluslarında normal over rezerv belirteçlerine rağmen yetersiz olgun oosit verimi gösteren beklenmedik düşük yanıt verenlerde (POSEIDON 1-2 grubu) artan gonadotropin başlangıç dozlarının OS sonuçları üzerindeki etkisini değerlendirdi.

Gereç ve Yöntemler: Bir referans infertilite kliniğinde yürütülen bu gözlemsel çalışmaya, ilk OS sikluslarında günlük 150-225 uluslararası birim (IU) gonadotropin dozları almasına rağmen dokuzdan az oosit toplayan kadınlar dahil edildi. Gebelik elde edemeyip ikinci bir OS siklusuna geçen kadınlar

PRECIS: Increasing gonadotropin starting doses improves oocyte yield and embryological outcomes in unexpected hypo-responders (POSEIDON 1-2) with suboptimal response, despite normal ovarian reserve markers.

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çalışmaya alındı. Vücut kitle indeksine göre gonadotropin başlangıç dozları 225 veya 300 IU rekombinant folikül uyarıcı hormon (FSH) (recFSH) olarak artırıldı. Her hasta, kendi tarihi kontrolü olarak değerlendirilerek, ilk ve ikinci OS siklusları karşılaştırıldı. Karşılaştırma, oosit verimi, foliküler çıktı oranı (FORT) ve folikül-oosit indeksi (FOI) üzerine odaklandı.

Bulgular: Çalışma süresince beklenmedik düşük yanıtlayıcı (POSEIDON 1-2) olarak tanımlanan toplam 289 kadın (%12 prevalans) belirlendi. Ortalama yaş 34,2 yıl ve ortalama anti-müllerian hormon seviyesi 3,4 ng/mL idi. Stimülasyon süresi her iki siklus arasında benzerdi (11,2 gün). Ancak ikinci OS siklusunda toplam oosit, metafaz II oosit, FORT, FOI, klivaj evresi embriyoları ve blastosist sayılarında anlamlı iyileşmeler gözlendi (p<0,05).

Sonuç: Sonraki sikluslarda gonadotropin dozlarının artırılması, normal over rezerv belirteçlerine sahip beklenmedik düşük yanıtlayıcılar (POSEIDON 1-2) için oosit verimini ve embriyolojik sonuçları iyileştirmektedir.

Anahtar Kelimeler: İnfertilite, ovülasyon indüksiyonu, *in vitro* oosit maturasyon teknikleri

Introduction

Ovarian stimulation (OS) is a cornerstone of assisted reproductive technology (ART), designed to recruit multiple follicles and obtain an adequate number of mature oocytes for embryo development. The number of mature oocytes retrieved is a key determinant of ovarian response to exogenous gonadotropins and is strongly correlated with cumulative live birth rates across fresh and frozen embryo transfer cycles[1].

Despite having normal ovarian reserve markers, some patients exhibit an unexpected hypo-response to OS, characterized by a suboptimal oocyte yield (<9) in their first cycle. This phenomenon has important implications for reproductive outcomes, as lower oocyte yields are associated with fewer available embryos, decreased cumulative live birth rates, and increased emotional and financial burdens for patients. While this condition is defined within the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) classification system, unexpected hypo responders constitute a distinct and increasingly recognized subgroup requiring targeted interventions to optimize ART success[2,3].

To assess unexpected hypo response, markers such as the follicular output rate (FORT) and follicle-to-oocyte index (FOI) provide valuable insights. These parameters evaluate the relationship between antral follicle count (AFC) and the number of retrieved oocytes, offering a more qualitative measure of ovarian responsiveness[4]. Patients with FORT or FOI values below 50% are typically classified as hypo-responders, highlighting the discrepancy between expected and actual ovarian response.

Determining the optimal gonadotropin dose for this subgroup is crucial for enhancing follicular recruitment, oocyte yield, and subsequent ART outcomes[5]. This study aims to investigate the impact of increasing the initial gonadotropin dose in patients who exhibited an unexpected hypo-response during their first OS cycle. By evaluating oocyte yield and secondary markers such as FORT and FOI in subsequent cycles, we aim to provide evidence-based guidance for optimizing stimulation protocols in this challenging patient population.

Materials and Methods

This observational study was conducted at a referral in vitro fertilization (IVF) center between October 2022 and September 2023. The study adhered to the principles of the Helsinki Declaration and was approved by the Üsküdar University Faculty of Medicine Ethics Committee on October 26, 2020 (protocol number: 61351342/OCTOBER 2022-24). Written informed consent was obtained from all participants.

Eligible patients included infertile women who exhibited an unexpected hypo response during their first OS cycle, defined as the retrieval of fewer than nine oocytes despite normal ovarian reserve tests (ORTs). Normal ORT was defined as serum anti-müllerian hormone (AMH) levels between 1-4 ng/mL and an AFC of 5-12 in both ovaries. The standard policy at the IVF center for initial gonadotropin dosing in patients with normal ORTs involved starting recombinant follicle-stimulating hormone (FSH) (recFSH) at 150 international unit (IU)/day for women with a body mass index (BMI) of 20-25 kg/m^2 or 225 IU/day for women with a BMI >25 kg/m^2[6-8].

Patients who underwent a second OS cycle within 12 months of the first cycle due to failure to conceive were included in this analysis. In the second OS cycle, a uniform dose escalation strategy was implemented to all patients. As a result, women with a BMI of 20-25 kg/m^2 received 225 IU/day of recFSH, while those with a BMI >25 kg/m^2 received 300 IU/day, beginning on the second day of the menstrual cycle. Each patient's first cycle served as a historical control for comparison of outcomes.

Exclusion criteria included patients with diminished ovarian reserve markers; failed follicular response during OS; presumed risk of ovarian hyperstimulation syndrome (total of >20 follicles measuring >12 mm on the day of hCG); inability to proceed with the second OS cycle; use of OS protocols other than GnRH antagonists; use of urinary gonadotropins; OS cycles involving dual ovulation triggering; preimplantation genetic testing for aneuploidy cycles; elevated serum progesterone (P) levels on the day of hCG administration; or an interval of more than 12 months between the two oocyte retrieval cycles.

The primary outcomes of this study were the FORT and FOI[9]. Secondary outcomes included the number of metaphase II (M2) oocytes retrieved and the number of good-quality embryos available.

OS was initiated using recFSH (Gonal-F, Merck Serono, Istanbul) on the second day of the menstrual cycle, without any pre-treatment such as oral contraceptives. A GnRH antagonist (Cetrotide, Merck Serono, Istanbul; 0.25 mg/day) was introduced on the sixth day of stimulation and continued

throughout the cycle. Final oocyte maturation was triggered with recombinant human chorionic gonadotropin (rhCG) (250 mcg; Ovitrelle, Merck Serono, Istanbul) when at least three follicles reached ≥18 mm in diameter. Transvaginal ultrasound-guided oocyte retrieval and subsequent embryo transfer procedures were conducted as previously described[10,11].

Results

During the study period, 289 women were identified as unexpected hypo responders based on their first OS cycle within a cohort of 2,390 infertile women, representing an overall prevalence of 12% (Figure 1). The median age of the participants was 34.00 years (24-42), with a median AMH level of 2.60 ng/mL (1.28-16.20) and an infertility duration of 5.00 years (1.00-22.00). Among these, 103 women (35.6%) underwent a second OS cycle, with a mean interval of 8.4 months between cycles. Demographic and clinical characteristics are summarized in Table 1.

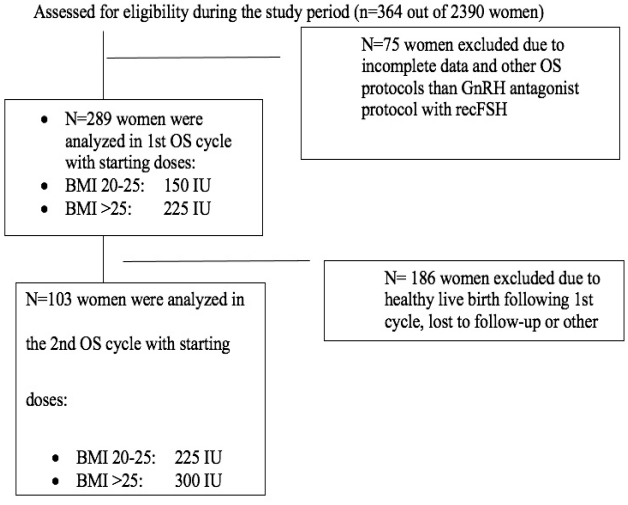

Figure 1. Flowchart of the study

OS: Oocyte stimulation, BMI: Body mass index, recFSH: Recombinant follicle-stimulating hormone, IU: International unit

Patients in the tailored gonadotropin dose group received significantly higher starting and total gonadotropin doses compared to the standard group (p<0.0001), while the stimulation duration remained comparable (p=0.26). Key ovarian response markers improved significantly, with higher median FORT (0.69 *vs.* 0.44, p<0.0001), FOI (0.67 *vs.* 0.38, p<0.0001), and total oocytes retrieved (9.00 *vs.* 5.00, p<0.0001) (Figures 2, 3).

Enhanced embryological outcomes were observed in the tailored dose group, including higher numbers of day 3 embryos (5.00 *vs.* 2.00, p<0.0001), day 5 embryos (3.00 *vs.* 2.00, p<0.0001), and top-quality blastocysts (2.00 *vs.* 0.00, p<0.0001), highlighting the benefits of dose escalation (Table 2, Table 3).

Discussion

This study demonstrates that tailored gonadotropin dose adjustments in unexpected hypo responders significantly improve oocyte yield, follicular response markers (FORT and FOI), and embryological outcomes, highlighting the importance of individualized OS protocols in optimizing ART success[5,6]. There is limited data on outcomes in POSEIDON groups 1b and 2b within Türkiye. A recent retrospective study

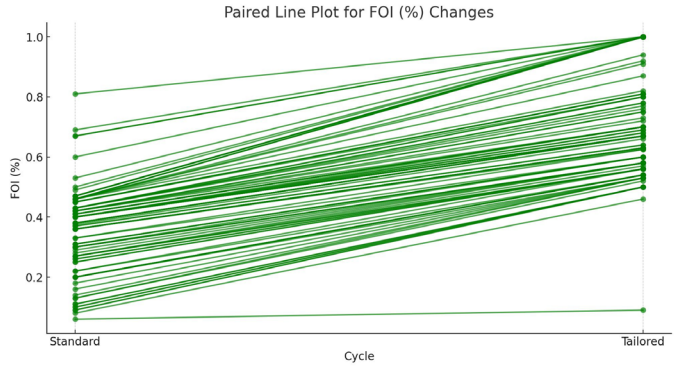

Figure 2. Paired line plot for FOI (%) changes

FOI: Follicle oocyte index

Table 1. Demographic data of standard and tailored groups

Parameter	Stat type	Standard group	Tailored group	p-value
Age (years)	Median (minimum, maximum)	34.00 (24.00, 42.00)	34.00 (24.00, 42.00)	0.982
Cause of infertility	1: 23% (unexplained) 2: 27% (male factor) 3: 16% (anovulatory) 4: 34% (other)			
Duration of infertility (years)	Median (minimum, maximum)	5.00 (1.00, 22.00)	6.00 (1.00, 22.00)	0.314
BMI (kg/m^2)	Median (minimum, maximum)	22.00 (18.00, 30.00)	22.00 (18.00, 30.00)	0.994
AFC (N)	Median (minimum, maximum)	11.00 (6.00, 19.00)	11 (6.00, 19.00)	0.580
AMH (ng/mL)	Median (minimum, maximum)	2.60 (1.28, 16.20)	2.71 (1.28, 16.20)	0.570

BMI: Body mass index, AFC: Antral follicle count, AMH: Anti-müllerian hormone

reported significantly lower live birth rates in this subgroup compared to normal responders, emphasizing the need for more personalized treatment strategies[7].

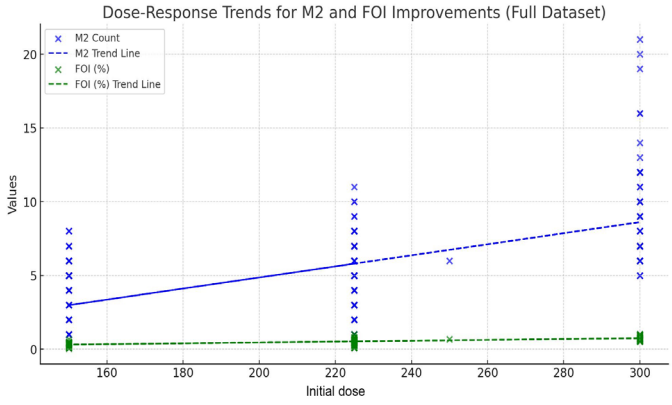

Figure 3. Dose-response trends for M2 and FOI improvements (full dataset)

FOI: Follicle oocyte index, M2: Metaphase II

Tailoring the FSH starting dose is typically guided by patient-specific characteristics and established ORTs. Individualized OS protocols have been supported by recent developments such as nomograms that assist clinicians in calculating daily FSH starting doses[8]. For women with normal ORTs, initial doses of 150-225 IU/day are commonly used, with the first ultrasound scan usually performed on the 5th or 6th day of stimulation. Subsequent dose adjustments, based on ovarian response, aim to prevent hypo-response or hyper-response. A recent systematic review reported that approximately 45% of cycles involved r-hFSH dose adjustments, with increases being more common than decreases[9]. However, it remains unclear whether initial doses or mid-cycle dose adjustments have a greater impact on follicular growth. Pharmacokinetic studies indicate that FSH reaches steady-state concentrations after 4–5 days of administration, with a biological response lag of approximately 4 days. This suggests that correct starting doses and fixed-dose regimens may better align with follicular dynamics than frequent dose adjustments, a hypothesis supported by recent data[10,11]. Further randomized controlled trials are needed to validate these findings[12].

Table 2. Ovarian stimulation outcomes of standard and tailored groups

Parameter	Stat type	Standard group	Tailored group	p-value
Peak serum estradiol (pg/mL)	Median (minimum, maximum)	1885.00 (273.00, 4228.00)	2866.50 (1000.00, 8534.00)	0.0000*
Gonadotropin starting dose (IU)	Median (minimum, maximum)	150.00 (150.00, 225.00)	300.00 (225.00, 300.00)	0.0000*
Total consumed gonadotropins (IU)	Median (minimum, maximum)	2250.00 (1050.00, 18750.00)	2925.00 (1800.00, 5100.00)	0.0000*
Total stimulation duration (day)	Median (minimum, maximum)	11.00 (6.00, 17.00)	11.00 (8.00, 17.00)	0.258
No of follicles >17 mm on trigger day	Median (minimum, maximum)	5.00 (1.00, 13.00)	9.00 (1.00, 22.00)	0.0000
FORT (%)	Median (minimum, maximum)	0.44 (0.08, 1.50)	0.69 (0.09, 1.50)	0.0000**
FOI (%)	Median (minimum, maximum)	0.38 (0.05, 0.81)	0.67 (0.09, 1.00)	0.0000*
No of COC	Median (minimum, maximum)	5.00 (1.00, 9.00)	9.00 (1.00, 20.00)	0.0000*
No of M2 oocytes	Median (minimum, maximum)	4.00 (1.00, 9.00)	7.00 (1.00, 21.00)	0.0000*
No of available day 3 embryos	Median (minimum, maximum)	2.00 (1.00, 9.00)	5.00 (1.00, 17.00)	0.0000*
No of available day 5 embryos	Median (minimum, maximum)	2.00 (0.00, 7.00)	3.00 (0.00, 10.00)	0.0000*
No of available top quality blastocysts	Median (minimum, maximum)	0.00 (0.00, 3.00)	2.00 (0.00, 5.00)	0.0000*

FORT: Follicular output ratio, FOI: Follicle oocyte index, COC: Cumulus oocyte complex, IU: International unit, M2: Metaphase II

Table 3. Comparison results for dose impact on M2 and FOI (%)

Metric	Group	Mean (95% CI)	p-value	Significant	Absolute difference (95% CI)
FOI (%)	Standard *vs.* tailored	0.34 (0.14, 0.54)	0.0000	Yes	0.34 (0.14, 0.54)
M2 count	Standard *vs.* tailored	3.88 (3.69, 4.08)	0.0000	Yes	3.88 (3.69, 4.08)

FOI: Follicle oocyte index, CI: Confidence interval, M2: Metaphase II

Higher gonadotropin doses improve oocyte yields, as shown in randomized control trials (RCTs) where dose increases of 50-100 IU resulted in significantly more oocytes, in unexpected responders and normal responders under 39 years[13-16]. While increasing gonadotropin doses may enhance ovarian response, studies indicate a potential increase in maternal complications, such as gestational diabetes mellitus and hypothyroidism, particularly in singleton pregnancies. This finding underscores the importance of individualized stimulation protocols[17]. Recent studies have shown that increasing recFSH doses by 50 IU increments improves oocyte retrieval outcomes in unexpected hypo-responders[12]. Our study confirmed these findings, with tailored dosing increases of 75-150 IU per patient and a maximum dose of 300 IU per day, resulting in significant improvements in oocyte yield and embryo outcomes[14,16]. This decision was based on our center's policy of not exceeding the generally accepted maximum dose of 300 IU/day to avoid diminishing returns and higher costs. However, recent evidence suggests that higher gonadotropin doses do not necessarily lead to an increased retrieval of MII oocytes. A machine learning model analyzing 9,598 ovarian stimulations demonstrated that excessive gonadotropin dosing may reduce oocyte yield in certain patient groups, reinforcing the importance of precise dosage optimization in clinical practice[18]. These findings highlight the benefits of tailored 'starting' dosing in unexpected hypo responders. While dose escalation may slightly increase costs, the higher number of embryos obtained enhances cumulative live birth chances, potentially making it a more cost-effective strategy. Differences in dose increments may reflect variations in patient BMI, which influences gonadotropin requirements. Until a consensus on optimal dose adjustments is established, decisions on escalation will depend on individual patient characteristics and clinical judgment.

The etiology of unexpected hypo response remains multifactorial, with emerging evidence pointing to genetic polymorphisms in gonadotropin receptors, such as the FSHR Ser680 allele and luteinizing hormone (LH)β variant, as significant contributors[19,20]. These polymorphisms are associated with altered gonadotropin receptor sensitivity, which may necessitate tailored stimulation approaches. In such cases, increasing gonadotropin doses or adding LH activity during OS has been suggested to improve follicular response and oocyte yield[20,21]. In a recent meta-analysis, significantly higher clinical pregnancy rates, implantation rates, and number of oocytes retrieved were observed in hypo-responders supplemented with recombinant LH versus hypo-responders who underwent FSH monotherapy[21]. However, no significant difference was observed between patients regarding the number of M2 oocytes retrieved. Therefore, there is a need for large controlled RCTs to provide robust evidence in this area.

Finally, variability in AFC measurements due to sonographer skill and ultrasound equipment differences poses a challenge in accurately identifying hypo-responders[8]. Nonetheless, the homogeneity of the study cohort minimizes some of these confounding factors, ensuring more reliable comparisons.

Study Limitations

The retrospective design of this study and the use of historical controls may introduce bias related to inter-individual variations. Additionally, dose adjustments were based on BMI and institutional protocols, which may limit the generalizability of the findings. Furthermore, the absence of an LH supplementation arm represents an additional limitation of this study.

Conclusion

Individualized gonadotropin dosing represents a promising approach for managing unexpected hypo responders, leading to enhanced ovarian response and improved embryological outcomes. Further randomized controlled trials are necessary to establish standardized protocols and optimize treatment strategies for this challenging patient subgroup.

Ethics

Ethics Committee Approval: The study was approved by the Üsküdar University Faculty of Medicine Ethics Committee on October 26, 2020 (protocol number: 61351342/OCTOBER 2022-24).

Informed Consent: All participants provided informed consent before entering the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.P, R.P., Concept: B.P.K., E.P, Design: E.P., B.P.K, Data Collection or Processing: G.İ, D.H.D., E.P, Analysis or Interpretation: B.P.K, E.P, Literature Search: B.P.K., G.İ., Writing: B.P.K., D.H.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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