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ORIGINAL RESEARCH

The Effect of the Gonadotropin Dose Increment During Controlled Ovarian Hyperstimulation on Live Birth Rates of POSEIDON Group 3-4 Patients

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ABSTRACT

This retrospective study seeks to explore whether modifying the gonadotropin dose in cases of poor ovarian response during controlled ovarian hyperstimulation contributes to improved live birth rates in Poseidon Group 3-4 patients. The study took place at a tertiary level university. The electronic database spanning 2012-2021 was scrutinized to identify patients with diminished ovarian reserve (DOR) who underwent intra-cytoplasmic sperm injection – embryo transfer (ICSI-ET). Diminished ovarian reserve was determined using the POSEIDON criteria. Patients were categorized into two groups based on whether dose adjustment was implemented during the initial ultrasound assessment in controlled ovarian hyperstimulation (COH). There were 188 patients in the dose adjustment (DA) group and 310 patients in the fixed-dose (FD) group. The demographic parameters were similar between the groups. The started gonadotropin dose was similar in both groups (300 IU). The median dose adjustment on the first control was +75 IU in the DA group. The follicle output rates, follicle to oocyte indexes, and the embryology parameters were comparable between the groups. The positive pregnancy rate was 19.7% (36/188) in the DA group vs. 19.1% (61/310) in the FD Group (p=0.4). The primary outcome of the study; live birth rates were 12% in the DA group vs. 9% in the FD group, and the results were statistically similar (p=0.3). Our research revealed that adjusting the gonadotropin dose in cases of inadequate ovarian response during COH results in comparable live birth rates to those observed in the fixed-dose group. For patients exhibiting an inadequate response, dose adjustment may be deemed necessary.

Key Words: Poor Ovarian Response. Diminished Ovarian Reserve. Gonadotropin Dosage. In vitro fertilization. Infertility.

Kontrollü Ovaryan Hiperstimülasyon Sırasında Gonadotropin Dozunun Artışının POSEİDON Grubu 3-4 Hastalarının Canlı Doğum Oranlarına Etkisi

ÖZET

Bu retrospektif çalışma, kontrollü ovaryan hiperstimülasyon sırasında düşük over yanıtı gösteren Poseidon Grubu 3-4 hastalarında gonadotropin dozunu değiştirmenin, canlı doğum oranlarını artırıp artırmadığını araştırmayı amaçlamaktadır. Çalışma üçüncü basamak bir üniversite hastanesinde gerçekleştirilmiştir. 2012-2021 yıllarını kapsayan elektronik veritabanı, düşük over rezervi (DOR) olan ve intra-sitoplazmik sperm enjeksiyonu - embriyo transferi (ICSI-ET) geçiren hastaları belirlemek için incelenmiştir. Düşük over rezervi, Poseidon kriterlerine göre belirlenmiştir. Hastalar, kontrollü over hiperstimülasyonu (COH) sırasındaki ilk ultrason değerlendirmesi sırasında doz ayarlamasının uygulanıp uygulanmadığına göre iki gruba ayrılmıştır. Doz ayarlaması (DA) grubunda 188 hasta ve sabit doz (FD) grubunda 310 hasta bulunmaktadır. Demografik parametreler gruplar arasında benzerlik göstermektedir. Başlangıç gonadotropin dozu her iki grupta da benzerdi (300 IU). İlk kontroldeki median doz ayarlaması DA grubunda +75 IU idi. FORT (follicle-output rate) oranları, folikül-oosit indeksleri ve embriyoloji parametreleri gruplar arasında karşılaştırılabilir düzeydeydi. Pozitif gebelik oranı DA grubunda %19,7 (36/188) iken, FD Grubunda %19,1 (61/310) idi (p=0,4). Çalışmanın birincil sonucu; canlı doğum oranları DA grubunda %12 iken, FD grubunda %9 olarak bulundu ve sonuçlar istatistiksel olarak benzerdi (p=0,3). Araştırmamız, kontrollü over hiperstimülasyonu sırasında yetersiz over yanıtı olan vakalarda gonadotropin dozunun ayarlanmasının, sabit doz grubunda gözlenen canlı doğum oranlarına benzer sonuçlar verdiğini ortaya koymuştur. Yetersiz yanıt gösteren hastalar için doz ayarlaması gerekli olabilir.

Anahtar Kelimeler: Düşük over rezervi. Kötü over yanıtı. Gonadotropin, in-vitro fertilizasyon. İnfertilite.

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Determining the optimal daily gonadotropin dosage for individuals undergoing controlled ovarian hyperstimulation (COH) in in vitro fertilization and intra-cytoplasmic sperm injection (IVF-ICSI) cycles poses a complex challenge for IVF practitioners. Various stimulation strategies have been developed, and numerous studies have explored the optimal daily gonadotropin dose for patients. Current data indicates that calculating the daily gonadotropin dose depends on factors such as age, ovarian reserve, body mass index (BMI), and previous stimulation outcomes[1].

For normo-responder patients, it is established that an adequate daily gonadotropin dosage falls within the range of 150-200 IU per day[2-4]. While this range typically suffices for optimal oocyte production, it may prove ineffective for poor responders. Clinicians often find it necessary to increase the daily gonadotropin dose in order to achieve the desired number of oocytes in poor responder patients. Despite some studies suggesting that a daily dose of 300 IU gonadotropin may be optimal for these patients, conflicting publications raise concerns about excessive stimulation (> 450 IU/day)[5,6].

Despite commencing with an optimal gonadotropin dose, the ovarian response may still be inadequate, necessitating intracycle dose adjustments in certain patients, as outlined by the recent POSEIDON classification[7]. The POSEIDON 3-4 subgroup, characterized by low anti-mullerian hormone (AMH) (< 1.2 ng/ml) and low antral follicle count (AFC) (< 5), particularly requires careful decision-making during COH.

Nevertheless, existing literature offers conflicting results on whether dose adjustments during COH improve pregnancy outcomes for POSEIDON 3-4 patients. In particular, there is a lack of data on dose increases for this group, including questions about how to increase, the amount of increase, the choice of gonadotropin, and the timing of the increase. Moreover, it remains unclear whether increasing the gonadotropin dose during COH, in the presence of an inadequate ovarian response, enhances live birth rates.

This study aims to investigate whether adjusting the gonadotropin dose in cases of inadequate ovarian response during COH improves live birth rates for POSEIDON Group 3-4 patients.

Material and Method

Study Design & Ethical Approval

This retrospective cohort study was conducted at a tertiary university hospital's Assisted Reproductive Technologies (ART) center. The study protocol received approval from the university's clinical trials ethical committee (Approval ID: 2023-13/31).

Patient Selection

Patients with diminished ovarian reserve (DOR) who underwent controlled ovarian hyperstimulation (COH) for intracytoplasmic sperm injection (ICSI) were identified from the electronic database of the ART center spanning the years 2012-2021. The POSEIDON criteria were utilized to identify DOR patients (those with low anti-mullerian hormone (AMH) <1.2 ng/ml and antral follicle count (AFC) <5)[7]. Inclusion criteria comprised women aged between 18-40 years, undergoing single-fresh good-quality blastocyst transfer (Gardner Class A or B)[8], without male factor infertility and endometrial pathology. To avoid bias, only one ICSI-ET cycle per patient was enrolled.

COH-ICSI-ET Protocol

All patients underwent routine infertility work-up. COH commenced on the 2nd or 3rd day of the menstrual cycle following a basal transvaginal ultrasound check. Daily gonadotropin dosage adjustments were made based on the patient's age, BMI, ovarian reserve, and previous COH history. Recombinant Follicle Stimulating Hormone (rFSH) or Human Menopausal Gonadotropin (HMG) was chosen based on clinician preference. The standard COH protocol employed a flexible antagonist protocol with hCG trigger. Triggering occurred when at least three follicles reached 17-18 mm. ICSI was performed for fertilization, and all patients underwent fresh single-day-5, good-quality blastocyst transfer. Vaginal micronized progesterone capsules (3x200 mg) were prescribed for luteal phase support post-oocyte retrieval, continued until a negative pregnancy test or the presence of fetal cardiac activity. A positive pregnancy test was defined as serum beta-hCG levels of 10 IU/L on the 9-10th day after embryo transfer, and live birth rate was determined as the singleton live birth after 24 weeks of pregnancy.

Interventions

Patients were categorized into two groups: Group A (Fixed Dose - FD Group) included patients without dose adjustments during the COH cycle, while Group B (Dose Adjustment Group – DA) comprised patients whose ovarian response was suboptimal at the first ultrasound check (at the 5th day of stimulation), leading to gonadotropin dose adjustments. Suboptimal ovarian response was defined as the presence of non-growing follicles during the initial ultrasound check. Recorded parameters included demographic factors (age, BMI, ovarian reserve tests (AMH-AFC)), COH cycle parameters, FORT (follicle output rate), FOI (follicle to oocyte index) scores, embryology parameters, and pregnancy outcomes (positive b-hCG (implantation) rate, miscarriage rate, live birth rate).

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (with 25th-75th percentiles), depending on the distribution. Categorical variables were expressed as percentages. Group comparisons utilized the independent samples t-test or Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. A two-sided p-value of 0.05 was considered statistically significant.

Results

A total 498 patients were enrolled in. There were 310 patients in the fixed-dose (FD) group and 188 patients in the dose adjustment (DA) group. The demographic parameters were similar between the groups (Age, Body Mass Index, Ovarian Reserve Parameters). The mean women age was 33.6 + 4.1 in the FD group and 33.8 + 4 in the DA group (p=0.6) (Table I). The started gonadotropin dose was similar in both groups (300 IU). The type of gonadotropin was mostly HMG in the DA group (48% in the FD vs. 67% in DA group, p=0.01). The median dose adjustment on the first control was +75 IU in the DA group, and the total gonadotropin consumption was significantly higher in the DA group, as expected (Median values; 3000 vs. 3900 IU, p<0.01). The follicle output rates, follicle to oocyte indexes, and the embryology parameters were comparable between the groups (number of picked up oocytes, metaphase-2 oocytes, and 2PN embryos). The positive pregnancy rate was 19.1% (61/310) in the FD Group vs. 19.7% (36/188) in the DA group (p=0.4). The primary outcome of the study; live birth rates were 9% in the FD group vs. 12% in the DA group and the results were statistically similar (p=0.3). (Table I)

We further analyzed the COH outcomes and the pregnancy results depending on the chosen gonadotropin type. There were 273 patients stimulated with HMG (147 in FD group vs. 126 in DA group) and 265 patients with rFSH (163 in FD group vs. 62 in DA group). The collected oocyte, metaphase 2 oocyte and two-pronuclei embryo numbers were comparable between the groups. (Table II) The pregnancy results did not change depending on gonadotropin type (Figure 1)

Table. I. Demographic Parameters, COH and Pregnancy Outcomes of Study Groups.

	Fixed Dose Group (FD) n=310	Dose Adjustment Group (DA) n=188	p
Age (years)	33.6 ± 4.1	33.8 ± 4	0.6
BMI (kg/m²)	24.7 ± 4.7	26.3 ± 4.7	0.06
AMH (ng/ml)	0.76 (0.37 – 1.17)	0.76 (0.41-1.2)	0.6
AFC	5 (3-7)	5 (3-7)	0.8
AFC on hCG day	5 (4-8)	6 (4-8)	0.6
E2 on hCG day	679 (352-1278)	709 (416-1291)	0.4
Total Gonadotropin Dosage (units)	3000 (2400-3750)	3900 (3150-4575)	<0.01
Start Gonadotropin Dosage (units)	300	300	0.2
Increased Gonadotropin Dosage (units)	-	75	
Gonadotropin Type FSH HMG	 52.6% - 163 47.4% - 147	 33% - 62 67% - 122	<0.01
Increased Gonadotropin FSH HMG LH	-	 20.7% - 39 69.8% - 129 10.5% -20	N/A
Duration of Stimulation (days)	10 (8-11)	11 (10-13)	<0.01
Increment Day	-	4 (5-9)	N/A
Duration after increment (days)	-	7 (5-9)	N/A
Oocyte	5 (2-8)	4 (2-7)	0.2
M2	3 (1-6)	3 (1-5)	0.6
2PN	2 (1-3)	2 (1-3)	0.5
FORT	114 (100-166)	100 (85-142)	0.1
FOI	80 (50-100)	79 (45-100)	0.1
Presence of cryo-preserved embryo	21.9% (68/310)	27.1% (51/188)	0.6
Positive b-hcG Rate	19.7% (61/310)	19.1% (36/188)	0.4
Miscarriage Rate	9.6% (30/310)	7% (13/188)	0.4
Ectopic Pregnancy Rate	1% (3/310)	-	N/A
Live Birth Rate	9% (28/310)	12% (23/188)	0.3

*BMI (body mass index), AMH (Anti-mullerian hormone), AFC (Antral Follicle Count), E2(Estradiol), FSH (Follicle Stimulating Hormone), HMG (Human Menopausal Gonadotropin), LH (Luteinizing Hormone), M2 (Metaphase Two Oocyte), 2PN (Two-Pronuclei Embryo), FORT (Follicle Output Rate), FOI (Follicle to Oocyte Index), N/A (Not Applicable)

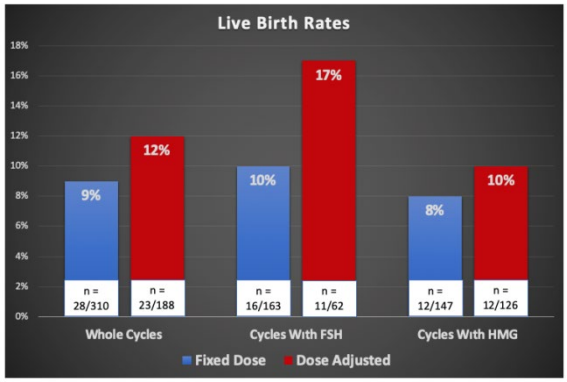
*Values are demonstrated with standard deviations, 25-75 percentiles or percentages

Table II. Comparison of COH outcomes depending on the used Gonadotropin Type

Gonadotropin Type FSH (n=225)	**Fixed Dose Group (FD) n=163**	**Dose Adjustment Group (DA) n=62**	**p**
No. of oocyte	5 (2-8)	6 (3-9)	0.1
No. of MII Oocyte	3 (1-6)	4 (2-7)	0.07
No. of 2PN	2 (1-4)	2 (1-4)	0.08
Gonadotropin Type HMG (n=273)	**Fixed Dose Group (FD) n=147**	**Dose Adjustment Group (DA) n=126**	**p**
No. of oocyte	4 (2-8)	4 (2-6)	0.1
No. of MII Oocyte	3 (1-5)	2 (1-4)	0.15
No. of 2PN	2 (1-3)	1 (1-2)	0.08

* COH (Controlled Ovarian Hyperstimulation) FSH (Follicle Stimulating Hormone), HMG (Human Menopausal Gonadotropin), LH (Luteinizing Hormone), MII (Metaphase Two Oocyte), 2PN (Two-Pronuclei Embryo),

*Values are demonstrated with standard deviations, 25-75 percentiles or percentages



*p values between the groups are not significant

Figure 1.
Live Birth Rates Depending on the Gonadotropin Type

Discussion and Conclusion

Encountering an unexpected poor ovarian response during controlled ovarian hyperstimulation (COH) poses challenges for both clinicians and patients. The available options are limited, with the potential course of cancelling the COH cycle, which, while preventing potential disappointment for the patient, may not be the most favorable outcome. Consequently, clinicians often find themselves compelled to consider increasing the daily gonadotropin dose. A large observational study involving 33,962 cycles in the USA reported that dose adjustment occurred in 41% of cycles, with 57.4% of these adjustments involving an increment in dose[9]. However, despite reports of dose adjustment occurring in up to 41% of cases, there remains insufficient evidence to recommend its routine application in clinical practice, and the current European Society of Human Reproduction and Embryology (ESHRE) guideline remains inconclusive regarding its impact on live birth rates[10]. With this knowledge gap in mind, we conducted this study, revealing that intracycle gonadotropin dose increments, in the presence of a poor ovarian response, yield similar live birth rates compared to cycles with an expected ovarian response in patients with diminished ovarian reserve.

Our study primarily focused on the POSEIDON Group 3-4 population (AMH <1.2 ng/dl and AFC < 5), a challenging subgroup that constitutes nearly half of the infertile population[11,12]. These patients present a considerable management challenge during COH, given their initial slow response to gonadotropin stimulation, as indicated by estradiol levels and follicle growth[13,14]. In this specific patient group, increasing the gonadotropin dose in response to a poor ovarian response at the initial ultrasound check may enhance the number of retrieved oocytes. While some studies, such as that of Drakopoulos et al., focused on intercycle dose adjustments, reporting that a 50 IU dose increment resulted in one more oocyte than the previous cycle[15], the significance of intracycle dose increments in improving live birth rates in patients with diminished ovarian reserve remains unclear.

Several studies, including a systematic review by Fatemi et al., have explored the impact of dose adjustments during ovarian stimulation, revealing an overall incidence of 45%, with a median day for dose increment permitted on Day 6 after the start of treatment[17]. However, no conclusive evidence supports the notion that dose adjustment is beneficial in cases of poor ovarian response. The randomized controlled study by Klinkert et al., focusing on poor responders, compared standard 150 IU gonadotropin dose to a fixed dose of 300 IU, concluding that higher gonadotropin doses or dose adjustments during COH did not improve pregnancy outcomes in this population[18]. Similarly, Aboulgar et al.'s randomized controlled trial in normoresponder patients with daily 300 IU gonadotropin dose reported that increasing the dose by 75 IU on antagonist day did not enhance pregnancy outcomes[19]. A retrospective analysis by Martin et al., encompassing all patients undergoing oocyte retrieval and fresh embryo transfer, found no apparent improvement in implantation rates or pregnancy outcomes when the daily dose of gonadotropins was increased during COH[20].

Our study contributes to this body of knowledge, indicating that whether recombinant FSH or human menopausal gonadotropin was used, the outcomes of COH did not significantly differ, supporting the current ESHRE guideline that both options are equally recommended in poor responders. Notably, both study groups demonstrated similar live birth rates (9% vs. 12%), suggesting that gonadotropin dose increments in the presence of a poor ovarian response result in comparable live birth rates to cycles with optimal ovarian responses. Without such dose increases, live birth rates might not have been equivalent. While the lack of a third study group without any dose increase, due to the retrospective nature of our study, limits the power of our results, a prospective randomized controlled study may provide additional strength. However, ethical considerations may hinder the design of a study involving a group without any intervention in inadequate ovarian response during stimulation. A limitation of our study is the lack of cumulative live birth rates, which would demonstrate the long-term effects of dose arrangements during the COH cycle. Our results indicated that the rate of cryo-preserved embryos was slightly higher in the DA group compared to the FD group; however, this difference was not statistically significant (21.9% vs. 27.1%, p=0.6).

An alternative treatment option for POSEIDON 3-4 patients is mild stimulation, a cost-effective approach

supported by numerous studies[21-24]. The American Society of Reproductive Medicine (ASRM) advised the use of mild stimulation (150 IU/day) in poor responder patients due to similar pregnancy outcomes compared to conventional doses[25]. A recent meta-analysis suggested that mild stimulation might be cost-effective, providing comparable live birth rates (12%)[26]. Even in mild stimulation, the possibility of dose increment remains an option in cases of inadequate ovarian response during stimulation.

While our study boasts a relatively high number of patients, homogenous distribution, and similar demographic parameters between study groups, its retrospective design imposes limitations on the robustness of our results. The absence of a third study group without any dose increase makes interpretation of the results challenging.

In conclusion, managing an unexpected poor ovarian response remains challenging, and despite current literature not advocating dose adjustments during COH cycles, our results suggest that intracycle gonadotropin dose increments may be beneficial in rescuing the cycle, particularly in cases of diminished ovarian reserve.

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Idea and design: G.U., I.K, K.A.; Data collection and processing: C.Ç, T.B.G, C.M. C.Ç, T.B.G, C.M.; Analysis and interpretation of data: K.A., I.K, B.A, G.U.; Writing of significant parts of the article: K.A.

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