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Age and dual trigger were found to be significant predictors of live birth in POSEIDON group 3 and 4 women treated with the GnRH antagonist protocol: a retrospective cohort study

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Abstract. – OBJECTIVE: Despite recent advancements in assisted reproductive technology (ART), the effective management of patients with poor ovarian response (POR) remains a formidable challenge. While various treatment strategies and predictors of live births have been documented to provide guidance to fertility specialists in managing poor responders, research efforts have predominantly encompassed all POSEIDON groups. In this study, our objective was to analyze the factors correlated with live births (LB) within a subset of the POSEIDON groups, with a particular focus on POSEIDON groups 3 and 4.

PATIENTS AND METHODS: Charts of 406 patients belonging to POSEIDON groups 3 and 4 who underwent ART treatment at a university-affiliated infertility clinic following a gonadotropin-releasing hormone (GnRH) antagonist cycle between January 2016 and December 2021 were analyzed. Clinically significant factors associated with live births were incorporated into a logistic regression model for multivariate analysis to ascertain independent predictors of LB. Additionally, a receiver operating characteristic (ROC) curve analysis was conducted to establish the optimal cut-off values.

RESULTS: Live births were achieved in 48 cycles (8.7%). Female age (OR, 0.930; 95% CI: 0.874-0.991; $p < 0.024$), baseline serum luteinizing hormone (LH) levels (OR, 0.854; 95% CI: 0.741-0.984; $p < 0.029$), and dual triggers (OR, 4.004; 95% CI: 1.290-12.426; $p < 0.016$) were identified as independent factors associated with LB following multivariate logistic regression analysis. The optimal age cut-off was determined to be 33 years, with a sensitivity of 70.8% and specificity of 75%.

CONCLUSIONS: Younger age, lower baseline serum LH levels, and dual-trigger administration appear to enhance the likelihood of live birth in POSEIDON groups 3 and 4 following treatments with the GnRH antagonist protocol.

Key Words:
POSEIDON criteria, Live birth, Poor ovarian response, Dual trigger, Female age.

Introduction

The field of assisted reproductive technology (ART) has witnessed notable advancements in recent years, offering new hope to couples encountering challenges in achieving successful pregnancies. However, the effective management of poor ovarian response (POR) poses a significant obstacle for both patients and clinicians. Globally, the prevalence of POR varies considerably, ranging from 5.6% to 35.1%[1]. This wide range can be attributed to the initial lack of consensus on the definition of POR. A systematic review[2] of studies focusing on patients with POR revealed 41 distinct definitions, each with differing criteria and thresholds. In an effort to standardize the definition of POR, the European Society for Human Reproduction and Embryology (ESHRE) introduced the Bologna criteria in 2011[3]. Nonetheless, criticism has been directed towards the Bologna criteria for their failure to account for the impact of age on oocyte quality, as well as the substantial heterogeneity observed within the population identified as having POR[4,5].

Consequently, researchers and clinicians from seven different countries collaborated to devise and publish the "Patient-Oriented Strategies Encompassing Individualized Oocyte Number" (POSEIDON) classification system for POR in 2016[6]. This new classification categorizes anticipated poor responders into four groups based on a combination of age and ovarian reserve markers, including risk factors unique to each

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patient, as well as the occurrence of poor ovarian responses to ovarian stimulation in previous ART cycles. Furthermore, the aim of this method is to promote personalized care for individuals with POR. From a practical standpoint, the POSEIDON classification system divides patients with POR into two main categories: the "unexpected POR" (groups 1 and 2) and the "expected POR" (groups 3 and 4).

The main differentiation between POSEIDON groups 3 and 4 pertains to the age of females: individuals under 35 years old are placed in group 3, while those aged 35 years or above are assigned to group 4. The selection of the age cut-off of 35 years is based on the reasoning that euploid blastocyst rates notably decline in patients beyond this age threshold[7]. Managing these patients, irrespective of age, can present challenges for clinicians owing to their elevated cycle cancellation rates, reaching nearly 50%[8,9]. While previous studies[10,11] have outlined management strategies and predictive factors for achieving live births in POSEIDON groups, these studies were relatively few in number and predominantly encompassed all POSEIDON groups. Consequently, further research is warranted to delineate the appropriate treatment protocols and predictive factors for live births within each specific POSEIDON group. The objective of the present study was to investigate the factors associated with live births in POSEIDON groups 3 and 4.

Patients and Methods

This retrospective cohort study reviewed the medical records of patients belonging to POSEIDON groups 3 and 4 who underwent treatment at a university hospital-based infertility clinic using a gonadotropin-releasing hormone (GnRH) antagonist protocol between January 2016 and December 2021. The Institutional Review Board of Ankara University, School of Medicine, Department of Obstetrics and Gynecology approved the study protocol (Decision No. 4, dated March 29, 2023). Additionally, all patients provided informed consent for anonymous utilization of their data for scientific purposes during their initial visit to the outpatient clinic.

Study Population

All participants in this study had to satisfy the following POSEIDON criteria to be classified as having a poor ovarian response: antral follicle count < 5 and/or serum anti-Müllerian hormone (AMH) level < 1.2 ng/mL. The inclusion criteria were i) female age ranging from 20 to 43 years, ii) meeting the criteria for POSEIDON groups 3 or 4[6], and iii) undergoing fresh embryo transfer. Exclusion criteria included pituitary downregulation with GnRH agonist protocols, diagnosis of any uncontrolled endocrine abnormalities (such as diabetes, hypo/hyperthyroidism, and hyperprolactinemia), presence of uterine anomalies at the time of embryo transfer, and male factor infertility attributable to azoospermia.

ART Protocol

On the second day of the menstrual cycle, ovarian stimulation (OS) commenced with either 225-300 IU/day of recombinant follicle-stimulating hormone (rFSH; GONAL-f, Merck Serono, Bari, Italy) alone or in combination with 150-225 IU/day of human menopausal gonadotropin (hMG; Menogon, Ferring GmBH, Kiel, Germany; or Menopur, Ferring GmBH, Kiel, Germany) with 150-225 IU/day of rFSH. Throughout the OS, adjustments to the gonadotropin dose were made based on the ovarian response, as assessed through transvaginal ultrasound scans and regular measurements of serum estradiol, progesterone, and luteinizing hormone (LH) levels. Upon reaching a leading follicle diameter of 14 mm, administration of 0.25 mg of the GnRH antagonist Cetrorelix (Cetrotide, Merck, Idron, France) commenced and continued until the day of final oocyte maturation triggering. The final oocyte maturation trigger was determined when at least 1-2 follicles attained a diameter ≥ 17 mm, employing one of the following regimens:

- 100 µg of choriogonadotropin alpha (Ovitrelle, Merck-Serono, Bari, Italy) combined with 0.2 mg of triptorelin acetate (Gonapeptyl, Ferring GmBH, Kiel, Germany).
- 250 µg of choriogonadotropin alpha (Ovitrelle, Merck-Serono, Bari, Italy).
- 0.2 mg triptorelin acetate (Gonapeptyl; Ferring GmbH, Kiel, Germany).

Transvaginal oocyte pick-up (OPU) was performed 36 h after the trigger. Standard intracytoplasmic sperm injection (ICSI) was performed on metaphase II (MII) oocytes.

During subsequent embryo monitoring, embryos at the cleavage stage were considered top-quality if they displayed four or five blastomeres on day 2 and at least seven blastomeres on day 3, with no multinucleated blastomeres and less

than 20% fragmentation on both days post-fertilization[12]. Embryos at the blastocyst stage were assessed based on Gardner and Schoolcraft's criteria[13], which evaluates both the developmental stage of the embryo (compaction stage, early blastocyst, full blastocyst, hatching blastocyst) and morphology of the trophoblast and inner cell mass. High-quality embryos were graded as AA, AB, BA, or BB, whereas low-quality embryos were graded as AC, CA, BC, CB, or CC. Preimplantation genetic testing for aneuploidy was not conducted for any of the embryos included in this study. Fresh embryo transfer (ET) was performed using embryos at either the cleavage stage (day 3) or blastocyst stage (day 5) under transabdominal ultrasound guidance. As per the national regulations governing embryo transfer policy, the procedure was limited to a maximum of two embryos at a time.

Starting on the day of oocyte retrieval, 300 mg/day of vaginal progesterone (Lutinus 100 mg vaginal tablets; Ferring GmbH, Kiel, Germany) was administered for luteal phase support. This was continued until the day of the serum pregnancy test (OPU+12 days). In cases with positive pregnancy test results, luteal support was extended until the 10th week of gestation.

The study aimed to identify factors associated with live births in women who are expected to have poor ovarian response. As a secondary outcome measure, the characteristics of the ovarian stimulation cycle and assisted reproductive technology (ART) outcomes were compared between POSEIDON groups 3 and 4. Clinical pregnancy was defined as the identification of a fetal heartbeat during an ultrasound scan at six weeks of gestation. Live birth was defined as the successful delivery of a live infant after at least 24 weeks of pregnancy.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows (version 20.0; IBM Corp., Armonk, NY, USA). Histograms and the Shapiro-Wilk test were used to assess the normal distribution of the data. Parametric tests were performed on the basis of these findings. The Student's *t*-test was used for the comparison of continuous variables, while categorical variables were compared using the Chi-squared test or Fisher's exact test, as appropriate. Clinically significant factors associated with live births were incorporated into a logistic regression model for multivariate analysis, with the results presented as adjusted odds ratios (OR) with a 95% confidence interval. The area under the receiver operating characteristic (ROC) curve (AUC) was computed to evaluate the accuracy of female age in predicting live births. Statistical significance was defined as $p < 0.05$.

Results

During the study period, 494 patients classified into POSEIDON groups 3 and 4 were treated at our center. Among them, 28 patients who underwent estrogen or progesterone priming and 32 patients treated with a GnRH agonist long protocol were excluded. Additionally, 13 patients with endocrinological abnormalities (10 with abnormal thyroid function tests and 3 with hyperprolactinemia) and 15 patients with uterine abnormalities were also excluded from the final analysis. Thus, data from 552 cycles in 406 patients were included in the analysis. Figure 1 illustrates the selection process for the study population.

In the study population, the mean age was 34.9 ± 3.5 years, and the mean body mass index (BMI) was 25.3 ± 3.2 kg/m^2. Apart from age, substantial differences were observed in the mean number of antral follicles, mean duration of infertility, and mean number of previous ART treatments between POSEIDON groups 3 and 4. However, baseline anti-Müllerian hormone (AMH) levels were comparable between the groups. Table I presents the demographics of the study population and a comparison of the baseline cycle characteristics of POSEIDON groups 3 and 4. The mean duration of stimulation and total dose of gonadotropin used were similar between the groups. Three different regimens were used to trigger final oocyte maturation, with similar utilization rates observed between the groups. Although the mean number of oocytes retrieved and the mean number of oocytes at the MII stage were higher in the POSEIDON group 3 patients, the mean number of embryos did not differ between the groups.

Within our sample, 238 cycles were canceled owing to various causes. Fertilization failure was the most common reason for cycle cancellation (51.3%; n = 122). We performed an oocyte pick-up (OPU) procedure in 436 (79%) cycles and had the opportunity to transfer an embryo in 314 (56.9%) cycles. There were no significant differences in the rates of clinical pregnancy, miscarriage, or live birth between POSEIDON groups 3 and 4, either per cycle or per embryo transfer (Table II).

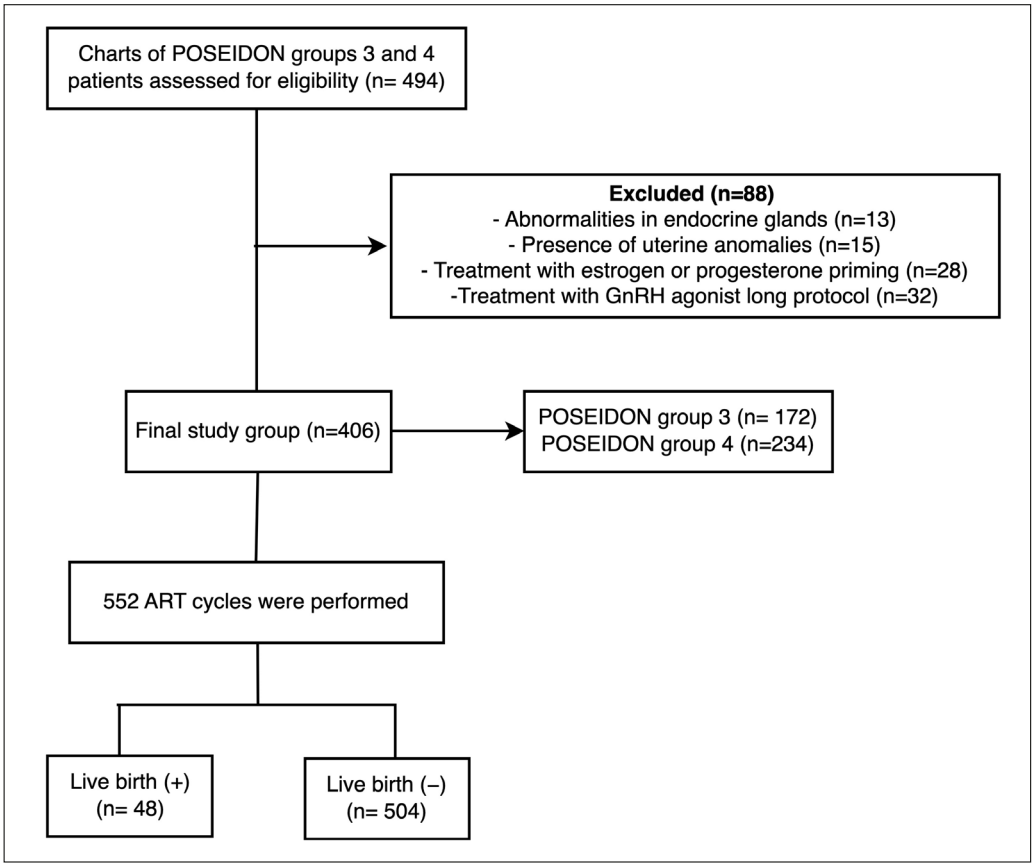

Figure 1. Flow chart of the study population.

Live births were achieved in 48 cycles (8.7%). Table III presents a comparison of the baseline and cycle characteristics of patients with and without live births. Statistically significant differences were observed between the two groups regarding female age, baseline serum LH levels, oocyte maturation-triggering method, endometrial thickness on the day of trigger, number of oocytes retrieved, number of oocytes in the MII stage, and number of embryos. Multivariate logistic regression analysis revealed that age (OR, 0.932; 95% CI: 0.874-0.991; $p = 0.024$), baseline serum LH levels (OR, 0.854; 95% CI: 0.741-0.984; $p = 0.029$), and dual triggers with human chorionic gonadotropin (hCG) and GnRH agonist (OR 5.331; 95% CI: 1.775-16.016; $p = 0.003$) were independent factors affecting live births in women with an expected POR (Table IV).

ROC analysis assessed the impact of various age values on the live birth rate, revealing an optimal cut-off for age at 33 years, exhibiting a sensitivity of 70.8% and a specificity of 75% (area under the curve, 0.749; 95% CI: 0.677-0.821; $p < 0.001$) (Figure 2).

Discussion

The current study aimed to delineate the factors linked with live births in patients anticipated to have a POR based on the POSEIDON classification undergoing treatment with a GnRH antagonist protocol. While clinical pregnancy and live birth rates were marginally higher in POSEIDON group 3 patients, this disparity did not reach statistical significance. Several factors have emerged as significant predictors of live birth. Notably, female age, baseline serum LH levels, and dual triggers were all identified as significant predictors of live births in the POSEIDON groups 3 and 4.

In individuals who are expected to have POR, the probability of achieving a live birth diminishes as the female age advances. This trend primarily stems from an increase in blastocyst aneuploidy rates associated with increasing female age[14]. Luo et al[15] examined embryo euploidy rates across four groups of women classified according to the POSEIDON criteria and identified comparable embryo euploidy rates between

Table I. Baseline characteristics and comparison of cycle characteristics between POSEIDON groups 3 and 4. Data are presented as mean ± standard deviation. $p < 0.05$ was considered statistically significant.

	POSEIDON group 3 (n = 172)	POSEIDON group 4 (n = 234)	*p*-value
Age (years)	29.5 ± 3.3	38.9 ± 3.6	< 0.001
BMI (kg/m^2)	25.1 ± 3	25.4 ± 3.3	0.342
Basal FSH (mIU/mL)	12.4 ± 8.1	12.8 ± 7.7	0.578
Basal LH (mIU/mL)	6.4 ± 6	5.9 ± 4.9	0.319
Basal estradiol (pg/mL)	51.4 ± 28	57.8 ± 65.9	0.238
TSH (mIU/L)	2 ± 1.2	2 ± 2	0.821
Prolactin (ng/mL)	16.2 ± 11	15.1 ± 10.9	0.353
AMH (ng/mL)	0.52 ± 0.35	0.45 ± 0.30	0.103
AFC, No.	4.1 ± 2	3.2 ± 1.9	< 0.001
Duration of infertility (years)	5 ± 3.4	6.5 ± 5.5	0.002
Previous IUI treatment, No.	0.8 ± 1.4	0.4 ± 0.9	0.001
Previous IVF/ICSI treatment, No.	0.7 ± 1.2	1 ± 1.6	0.040
Male factor, n (%)	58 (33.7%)	56 (23.9%)	0.034
Duration of stimulation (days)	10.6 ± 3.7	10.8 ± 4.3	0.731
Total dose of gonadotrophins (IU)	2,538 ± 1,318	2,478 ± 1,321	0.606
Total dose of rFSH (IU)	1,299 ± 1,359	1,255 ± 1,257	0.703
hMG use on OS, n (%)	168 (80%)	286 (83.6%)	0.279
Final oocyte maturation triggering method, n (%)			0.332
- hCG-only trigger	156 (79.6%)	242 (76.1%)	
- GnRH- agonist only trigger	36 (18.4%)	62 (19.5%)	
Dual trigger	4 (2%)	14 (4.4%)	
EMT on day of trigger (mm)	10.4 ± 2	9.9 ± 1.7	0.095
Estradiol levels on day of trigger (pg/mL)	651 ± 515	494 ± 391	< 0.001
No. of oocytes retrieved	2.8 ± 2.6	2.2 ± 2	0.006
No. of MII oocytes	2 ± 2.4	1.4 ± 1.5	0.001
No. of embryos	1.2 ± 1.6	1 ± 1.1	0.141
No. of transferred embryos	1.1 ± 0.3	1.4 ± 0.5	< 0.001

BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; AMH, anti-Müllerian hormone; AFC, antral follicle count; IUI, intrauterine insemination; IVF, in-vitro fertilization; ICSI, intracytoplasmic sperm injection; rFSH, recombinant follicle-stimulating hormone; hMG, human menopausal gonadotropin; OS, ovarian stimulation; hCG, human chorionic gonadotropin; GnRH, gonadotropin releasing hormone; EMT, endometrial thickness; MII, second metaphase.

POSEIDON groups 1 and 3. This underscores the significance of age on oocyte quality, rather than ovarian reserve, in patients with POR. Li et al[11] analyzed the predictive factors for live birth in fresh treatment cycles in all POSEIDON groups. According to their findings, female age has emerged as an independent predictor of live birth. Interestingly, they observed a significant

Table II. Reproductive outcome characteristics of POSEIDON groups 3 and 4 per started cycle. $p < 0.05$ was considered statistically significant.

	POSEIDON group 3 (n = 210)	POSEIDON group 4 (n = 342)	*p*-value
Per started cycle			
Pregnancy rate	32 (15.2%)	46 (13.5%)	0.318
Clinical pregnancy rate	30 (14.3%)	38 (11.1%)	0.232
Live birth rate	24 (11.4%)	24 (7%)	0.074
Miscarriage rate	6 (2.9%)	14 (4.1%)	0.450
Per embryo transfer			
Pregnancy rate	32 (25%)	46 (24.7%)	0.957
Clinical pregnancy rate	30 (23.4%)	38 (20.4%)	0.452
Live birth rate	24 (18.8%)	24 (12.9%)	0.157
Miscarriage rate	6 (4.7%)	14 (7.5%)	0.311

Table III. Baseline and cycle characteristics of patients with live birth and non-live birth. Data are presented as mean ± standard deviation. $p < 0.05$ was considered statistically significant.

	LB group (n = 48)	non-LB group (n = 504)	*p*-value
Age (years)	33.5 ± 4.1	35.7 ± 5.9	0.012
BMI (kg/m^2)	25 ± 3	25.2 ± 3.2	0.646
Duration of infertility (years)	4.6 ± 3.9	5.9 ± 5.1	0.081
Basal FSH (mIU/mL)	11.2 ± 4.9	13 ± 7.9	0.154
Basal LH (mIU/mL)	4.4 ± 2.5	6.3 ± 5.3	0.024
Basal estradiol (pg/mL)	49.8 ± 17.7	54.5 ± 50.5	0.544
TSH (mIU/L)	1.6 ± 1	2 ± 1.9	0.171
Prolactin (ng/mL)	13.3 ± 5.6	16.3 ± 11.4	0.120
AMH (ng/mL)	0.55 ± 0.28	0.47 ± 0.33	0.175
AFC, no.	4 ± 1.6	3.5 ± 2	0.124
Male factor, n (%)	14 (29.9)	128 (25.4)	0.568
Duration of stimulation (days)	10.3 ± 2.7	10.8 ± 4.2	0.517
Total dose of gonadotrophins (IU)	2,407 ± 1,261	2,510 ± 1,325	0.607
Total dose of rFSH (IU)	1,284 ± 1,261	1,271 ± 1,300	0.703
hMG use on OS, n (%)	38 (79.2)	416 (82.5)	0.559
Oocyte maturation triggering method, n (%)			< 0.001
- hCG-only trigger	30 (71.4)	368 (78)	
- GnRH- agonist only trigger	6 (14.3)	92 (19.5)	
- Dual trigger	6 (14.3)	12 (2.5)	
No. of follicles > 14 mm on day of oocyte retrieval	3.5 ± 1.8	2.5 ± 1.7	< 0.001
No. of follicles > 17 mm on day of oocyte retrieval	2 ± 0.9	1.6 ± 1.1	0.021
EMT on day of embryo transfer (mm)	11.4 ± 2.2	10 ± 1.7	< 0.001
Estradiol levels on day of trigger (pg/mL)	686 ± 364	545 ± 454	0.098
No. of oocytes retrieved	3.4 ± 1.5	2.3 ± 2.3	0.002
No. of MII oocytes	2.7 ± 1.3	1.6 ± 1.9	< 0.001
No. of embryos	1.8 ± 0.8	1 ± 1.4	< 0.001
No. of transferred embryos	1.4 ± 0.5	1.3 ± 0.4	0.054
Stage of transferred embryos, n (%)			0.207
- Cleavage	42 (87.5)	247 (92.9)	
- Blastocyst	6 (12.5)	19 (7.1)	

BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; AMH, anti-Müllerian hormone; AFC, antral follicle count; rFSH, recombinant follicle-stimulating hormone; hMG, human menopausal gonadotropin; OS, ovarian stimulation; hCG, human chorionic gonadotropin; GnRH, gonadotropin releasing hormone; EMT, endometrial thickness; MII, second metaphase.

decline in the likelihood of live births when the female age exceeded 34 years, a threshold lower than the age cut-off specified in the POSEIDON classification system. In line with this study, we identified the optimal cutoff point for predicting live births as 33 years in our current research, which once again falls below the age criteria outlined in the POSEIDON classification. These results underscore the ongoing importance of age in influencing live births in the POSEIDON group. Despite the age threshold of 35 years being established based on changes in blastocyst euploidy rates, our findings indicate that the effect of age on live birth rates does not align with

Table IV. Multivariate logistic regression analysis of factors related to live birth. $p < 0.05$ was considered statistically significant.

Variable	OR	95% CI	*p*-value
Age (years)	0.930	0.874-0.991	0.024
Basal LH (mIU/mL)	0.854	0.741-0.984	0.029
Oocyte maturation triggering method			
- hCG-trigger	Reference		
- GnRH- agonist only trigger	0.663	0.253-1.735	0.403
- Dual trigger	4.004	1.290-12.426	0.016

LH, luteinizing hormone; hCG, human chorionic gonadotropin; GnRH, gonadotropin releasing hormone.

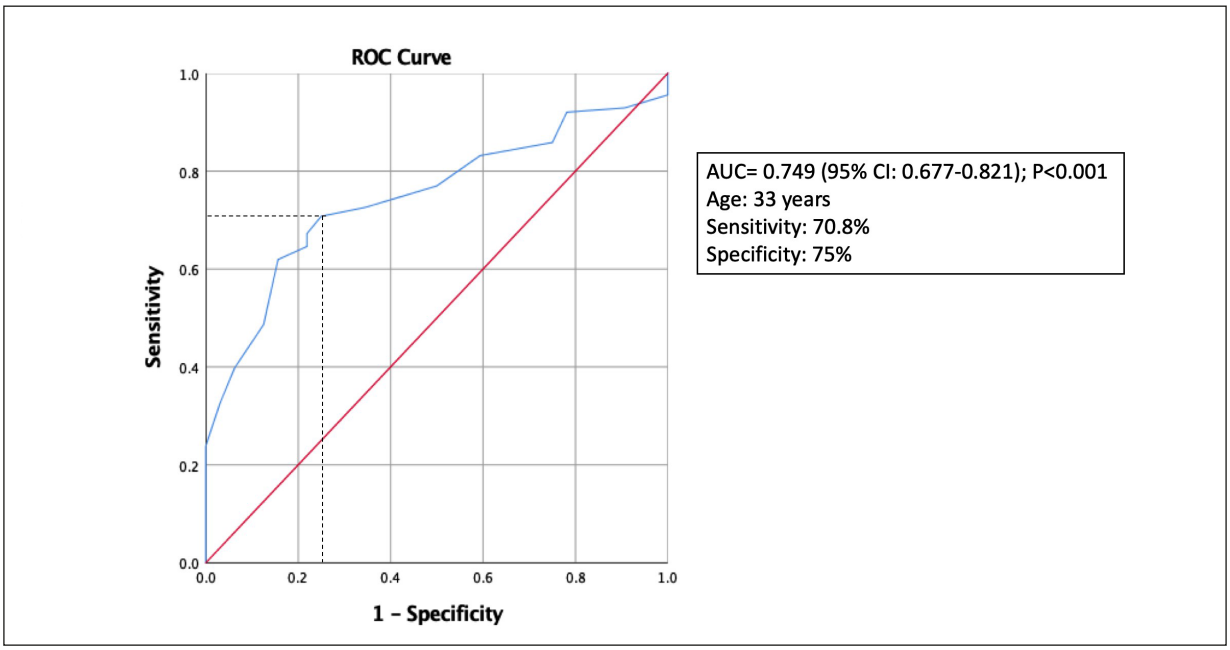

Figure 2. Receiver operating characteristics (ROC) curve for prediction of live birth using female age. The optimal cut-off value for age was found to be 33 years, with 70.8% sensitivity and 75% specificity.

this threshold. Therefore, it may be advisable to consider a lower age limit when providing counseling and designing treatment strategies for women with a poor ovarian response.

In the early 2000s, several studies[16,17] were conducted to assess the predictive value of baseline serum LH levels for the success of IVF/ICSI procedures. However, these studies found that basal serum LH levels were not an effective predictor of treatment success. In contrast, recent studies[18,19] have focused on evaluating the impact of serum LH levels at various points during ovarian stimulation on treatment outcomes rather than solely measuring serum LH levels at the beginning of the cycle. However, in 2021, Weng et al[20] published an article demonstrating an association between baseline serum LH levels and GnRH receptor (GnRHR) polymorphisms, particularly in women in POSEIDON groups 3 and 4. A single nucleotide polymorphism (SNP) in the GnRH receptor (GnRHR) was identified in patients exhibiting elevated baseline serum LH levels. Although the precise mechanism by which this alteration affects the protein structure or function of GnRHR remains unknown, its detrimental impact on endometrial receptivity and embryo development may have contributed to the observed lower live birth rates among individuals with high basal LH levels in our study. As more genetic studies have been published[21,22], particularly those focusing on the influence of SNPs on GnRHR function, a clearer understanding of the exact relationship between baseline serum LH levels and treatment outcomes will emerge.

Final oocyte maturation triggering (OT) may seem simpler than ovarian stimulation (OS), yet the significance of an individualized approach should not be overlooked at this stage of treatment. The primary agents used for OT are human chorionic gonadotropin (hCG) and GnRH agonists (in GnRH antagonist cycles). Despite their similar intended use, the key distinction in their mechanism of action lies in the absence of follicle-stimulating hormone (FSH) flares observed with GnRH agonists, which are not present with hCG. Oocytes require the presence of both FSH and LH for the successful completion of meiosis 1[21,22]. Furthermore, FSH not only induces ovulation but also influences cumulus expansion and oocyte maturation[23,24]. Nonetheless, a significant drawback of the GnRH agonist (GnRHa) trigger is the necessity for modified luteal phase support owing to the shorter duration of the LH surge[25]. Dual-trigger and double-trigger OT are two novel OT methods that have recently been introduced into clinical practice. These innovative approaches have the potential

to optimize ART outcomes by enhancing follicular function, oocyte meiotic maturation, and cumulus expansion[26]. In the dual-trigger method, simultaneous administration of low-dose hCG and GnRHa occurs. Dual triggers were selected for a small subset of patients (n = 18/542, 3.3%) in our study; nevertheless, the live birth rate in this group was 33%. Sloth et al[27] conducted a systematic review and meta-analysis of the impact of dual triggers on reproductive outcomes in low responders by 2022. Their findings revealed a favorable effect of the dual trigger on clinical pregnancy and live birth rates compared to the hCG trigger. Following this review, Tulek et al[28] documented ART treatment outcomes in nearly 3,000 POSEIDON groups of 3 and 4 patients. The group utilizing dual-triggering exhibited significantly higher numbers of retrieved oocytes, MII oocytes, oocyte maturation rates, fertilization rates, implantation rates, clinical pregnancy rates, and live birth delivery rates than the hCG-only group. Based on our findings and those of the literature, the impact of dual triggers on reproductive outcomes in women with a poor ovarian response appears promising. However, it is important to note that all the aforementioned studies, including ours, had a retrospective design. Therefore, these findings should be validated in large-scale prospective studies.

The present study represents one of the first attempts to examine the factors influencing live births in POSEIDON groups 3 and 4 patients undergoing treatment with the GnRH antagonist protocol. However, the retrospective design of our study was a significant limitation, potentially introducing bias in patient selection. Another limitation was the exclusive inclusion of patients undergoing fresh embryo transfer, which may limit the generalizability of our results to patients undergoing frozen embryo transfer.

Conclusions

In the current study, younger age, low baseline serum LH levels, and dual triggers emerged as independent factors influencing live births in POSEIDON groups 3 and 4. It is crucial to recognize that the patients in this study exclusively underwent the GnRH antagonist treatment protocol, with dual triggers administered to only a limited number of patients. Prospective large-scale studies encompassing diverse treatment protocols are essential to precisely delineate the factors affecting assisted reproductive technology treatment outcomes in this complex patient cohort.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval

The Institutional Review Board of Ankara University, School of Medicine, Department of Obstetrics and Gynecology approved the study protocol (Decision No. 4, Dated 29 March 2023).

Informed Consent

At their first admission to the outpatient clinic, all patients provided informed consent for the anonymous use of their data for scientific purposes.

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Authors' Contributions

Conception and design of the study: Yavuz Emre Şükür, Bülent Berker; Acquisition of data: Batuhan Özmen, Murat Sönmezer, Cem Atabekoğlu, Ruşen Aytaç; Analysis and interpretation of data: Yavuz Emre Şükür, Bulut Varlı; Drafting the article: Bulut Varlı, Batuhan Özmen, Murat Sönmezer, Cem Atabekoğlu, Bülent Berker; Supervision: Ruşen Aytaç. All authors have read and agreed to the published version of the manuscript.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available because of privacy and ethical restrictions but are available from the corresponding author upon reasonable request.

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