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Is Anti-mullerian Hormone Level an Important Marker for Predicting Live Birth in Patients with Diminished Ovarian Reserve?

Azalmış Over Rezervi Olan Hastalarda Canlı Doğumu Öngörmede Anti-müllerian Hormon Düzeyi Önemli Bir Belirteç midir?

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ABSTRACT

Objective: Diminished ovarian reserve (DOR) poses a significant challenge in infertility treatment. Anti-Müllerian hormone (AMH) is an important indicator of ovarian reserve and has been linked to live birth outcomes in assisted reproductive technologies (ART). This study aims to evaluate the factors most significantly impacting live birth (LB) rates in patients with DOR. **Materials and Methods:** This retrospective cohort study included 195 DOR patients undergoing intracytoplasmic sperm injection (ICSI) between 2020 and 2023. Patients were divided into "LB" (n=26) and "non-LB" (n=169) groups. Parameters such as age, antral follicle count (AFC), basal hormone levels, AMH, number of oocytes retrieved, embryo quality, and endometrial thickness were analyzed using univariate and multivariate logistic regression. ROC analysis was applied to assess the predictive value of these factors for LB outcomes. **Results:** AMH was identified as the most significant predictor of LB, with a cut-off value of 0.93 ng/mL. Other factors such as age, AFC, and endometrial thickness showed limited predictive accuracy. Frozen embryo transfer (FET) cycles were significantly associated with higher LB rates compared to fresh embryo transfers (OR=4.33, p=0.008). **Conclusion:** AMH levels are a key predictor of LB in DOR patients, particularly in POSEIDON 3-4 groups. The findings support the use of individualized treatment strategies, with FET being associated with improved LB outcomes in this patient population. Further research is needed to optimize ART protocols for patients with DOR.

Keywords: Antimullerian hormone; ovarian reserve; pregnancy outcome; live birth

ÖZET

Amaç: Azalmış over rezervi (DOR) infertilite tedavisinde önemli bir zorluk teşkil etmektedir. Anti-Müllerian hormon (AMH) over rezervinin önemli bir göstergesidir ve yardımcı üreme teknolojilerinde (YÜT) canlı doğum sonuçlarıyla ilişkilendirilmiştir. Bu çalışmanın amacı, DOR hastalarında canlı doğum (LB) oranlarını en çok etkileyen faktörleri değerlendirmektir. **Gereç ve Yöntemler:** Bu retrospektif kohort çalışmasına 2020-2023 yılları arasında intrasitoplazmik sperm enjeksiyonu (ICSI) uygulanan 195 DOR hastası dahil edilmiştir. Hastalar “canlı doğum” (n=26) ve “canlı doğum olmayan” (n=169) gruplara ayrılmıştır. Yaş, antral folikül sayısı (AFC), bazal hormon seviyeleri, AMH, alınan oosit sayısı, embriyo kalitesi ve endometriyal kalınlık gibi parametreler tek değişkenli ve çok değişkenli lojistik regresyon kullanılarak analiz edilmiştir. Bu faktörlerin LB sonuçları için öngörücü değerini değerlendirmek için ROC analizi uygulandı. **Bulgular:** AMH, 0.93 ng/mL kesme değeri ile LB'nin en anlamlı öngörücüsü olarak belirlendi. Yaş, AFC ve endometriyal kalınlık gibi diğer faktörler sınırlı öngörü doğruluğu göstermiştir. Dondurulmuş embriyo transferi (FET) döngüleri, taze embriyo transferlerine kıyasla daha yüksek LB oranları ile anlamlı şekilde ilişkiliydi (OR=4.33, p=0.008). **Sonuç:** AMH düzeyleri, DOR hastalarında, özellikle POSEIDON 3-4 gruplarında LB'nin önemli bir belirleyicisidir. Bulgular, FET'in daha iyi LB sonuçları ile ilişkili olduğu bireyselleştirilmiş tedavi stratejilerinin kullanımını desteklemektedir.

Anahtar Kelimeler: Antimüllerian hormon; gebelik sonucu; over rezervi; canlı doğum

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DOR refers to the reduction in the quantity and quality of oocytes available in the ovaries. This condition can be a significant factor in fertility and reproductive health, affecting the chances of natural conception and the success rates of ART. DOR is found in 10-30% of infertility cases, posing a considerable challenge.[1] In this challenging patient group, which presents difficulties for infertility professionals, numerous clinical studies have been conducted. These studies aim to predict clinical outcomes and LB rates, as well as to help determine the ideal medication protocol.[2-5]

In women, there is a reduction in both the number and the health of oocytes available, typically occurring around the age of 40, is a normal physiological process. However, some women encounter an unusually early decline in ovarian reserve, leading to premature infertility. This condition, which typically occurs young, is often idiopathic.[6] The primary clinical features of DOR include regular menstrual cycles accompanied by abnormal ovarian reserve test results, though not yet reaching postmenopausal levels. The most commonly assessed and widely used criteria to define DOR include the AFC and the serum levels of AMH and follicle-stimulating hormone (FSH).[7] AMH, which is secreted by primary and antral follicles, serves both autocrine and paracrine roles in controlling the maturation of follicles.[8] AMH levels consistently rise, reaching a peak and stabilizing around the age of 25; thereafter, the levels in the serum start to decrease.[9]

In 2016, the POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) classification was introduced, categorizing DORs into four subgroups based on age, AFC, prestimulation ovarian reserve tests, and previous cycle outcomes. Practically, this classification differentiates between two primary categories: the ‘expected’ DORs (groups 3 and 4) and the ‘unexpected’ DORs (groups 1 and 2). The goal of the POSEIDON criteria is to direct individualized treatment approaches for second and future cycles.[10] DOR is linked to adverse reproductive outcomes, including higher rates of embryonic aneuploidy, low LB rates, fertilization failure, and an increased risk of miscarriage.[11] Therefore, studies that contribute to the literature are crucial for improving LB rate in patients with DOR. The objective of this research is to determine the clinical data that most significantly impacts LB in patients with POSEIDON 3-4, contributing to the literature, and to provide more detailed information to individuals in this patient group with data that can predict LB.

MATERIAL AND METHODS

This retrospective cohort study was approved by the local Ethics Committee of the University of Sciences Konya City Hospital (Date: 02.10.2024, number: 12-35). Our study was conducted in accordance with the principles of the Declaration of Helsinki. The patients included in the study provided both written and verbal consent. We accessed patient data from computer records and infertility files for individuals who underwent the ICI procedure due to DOR at the IVF unit of Konya City Hospital between the years 2020 and 2023. Expected DOR patients (POSEIDON 3-4, AMH <1.2 ng/mL, AFC<7) were included in the study. Patients with previous oophorectomy or ovarian surgery, endometrioma/endometriosis, male infertility with low ovarian reserve, and additional systemic diseases were excluded from the study.

We analyzed the demographic and cycle characteristics of 195 DOR patients in the “LB group (n=26)” and “non-LB group(n=169)” and identified the statistically significant factors that influenced the LB outcomes. Univariate and multivariate logistic regression analysis was applied to evaluate the parameters that may affect LB. We analyzed parameters most relevant to LB such as, age, basal levels of FSH, LH (luteinizing hormone), E2 (estradiol), AMH, total oocytes retrieved, M2 oocytes, total number of embryos formed, number of transferred embryos, endometrial thickness on the day of transfer, FET cycles, embryo quality (Grade 1,2 ,3).

OVARIAN STIMULATION PROTOCOL

Women participated in ICSI cycles following a multidose flexible GnRH antagonist protocol. Ovarian stimulation was performed at the physician’s discretion using 225-300 IU of recombinant FSH (Gonal-F, Merck, İstanbul, Türkiye) and 75-150 IU of hp-HMG (Menopur, Ferring, İstanbul, Türkiye). Regular serum

E2 measurements and transvaginal ultrasounds were used to closely monitor the ovarian response. Once the follicle diameter reached 12-13 mm, a GnRH antagonist (Cetrotide, Merck, İstanbul, Türkiye) was administered. Rec-hCG (Ovitrelle, Merck, İstanbul, Türkiye) was administered once at least one follicle exceeded a diameter of 17 mm. Oocyte retrieval took place under general anesthesia, utilizing vaginal ultrasound guidance to puncture the follicles, 34 to 36 hours following hCG administration. All patients underwent standard ICSI procedure with the highest quality and M2 oocytes. Zygotes were incubated and developed to the blastocyst stage. Embryo grading was performed based on the number and uniformity of blastomeres, as well as the percentage of fragmentation (Grade 1, 2,3). In patients with an early elevation in progesterone levels on the hCG day (i.e., >1 ng/ml), along with a thin endometrium and intrauterine fluid accumulation, embryo cryopreservation was performed. FET was conducted during a hormone replacement therapy cycle. The number of embryos transferred was determined through a shared decision-making process in accordance with national guidelines. Embryo transfer was conducted in every case with a soft catheter under ultrasound guidance. For luteal phase support, a 600 mg daily vaginal progesterone capsule (Progestan, Koçak Farma, İstanbul, Türkiye) was administered and continued until a fetal heartbeat was detected on ultrasound. Live birth was defined as the birth of a living infant after 24 weeks of gestation.

STATISTICAL ANALYSIS

We evaluated the data using SPSS 26 and Jamovi programs. Normality distribution was evaluated by Kolmogorov-Smirnov test and histograms. T test between independent groups was used for pairwise comparisons of continuous data and the results were presented as mean±standard deviation. Chi-square test was used to compare categorical data and the results were expressed as percentage (%). Univariate and multivariate logistic regression analysis was applied to evaluate the parameters that may affect LB (parameters used: age, FSH, AMH, total oocytes, M2 oocytes, total embryos, endometrial thickness on the day of transfer, FET, double embryo transfer, embryo quality [1-3, 2-3, 1-2]). Variables included in the multivariate regression analysis were selected based on both statistical and clinical considerations. First, variables with a p-value <0.10 in univariate analysis were considered candidates for inclusion in the multivariate model. Additionally, variables known to be clinically relevant in predicting LB outcomes, such as age, FSH, AMH, total oocyte count, embryo quality, endometrial thickness, and FET, were also included. To prevent multicollinearity, a variance inflation factor (VIF) test was applied, and variables with high intercorrelation were excluded. The final model was constructed using a backward stepwise elimination approach, retaining only variables that remained statistically significant in the multivariate analysis. ROC analysis was applied to analyze the parameters predicting LB (AMH, total number of oocytes, number of M2 oocytes, total number of embryos formed, endometrial thickness on the day of transfer, AFC) and the results were presented with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC). A statistical significance level of p<0.05 was accepted.

RESULTS

In total, 195 IVF patients with DOR were included in the study. There was no significant difference between the LB and non-LB groups in terms of BMI, AFC, LH, E2, total gonadotropin dose, progesterone levels on the day of hCG administration and endometrial thickness on the day of embryo transfer (p > 0.05). However, the mean age of the LB group was significantly lower (p = 0.045). FSH levels were lower (p=0.022) and AMH levels were higher (p=0.001) in this group (Figure 1). In addition, the number of oocytes collected (p=0.019), the number of M2 oocytes (p=0.023) and the total number of embryos formed (p=0.006) were statistically higher in the LB group. This group was characterized by a thicker endometrial lining on the day of transfer (p=0.015) and more frequent FET application. In terms of embryo quality, the LB group had a higher proportion of Grade 1 embryos (41.02% vs. 26.28%; p=0.008), while the non-LB group contained more Grade 3 embryos (30.94% vs. 7.70%; p=0.008). The

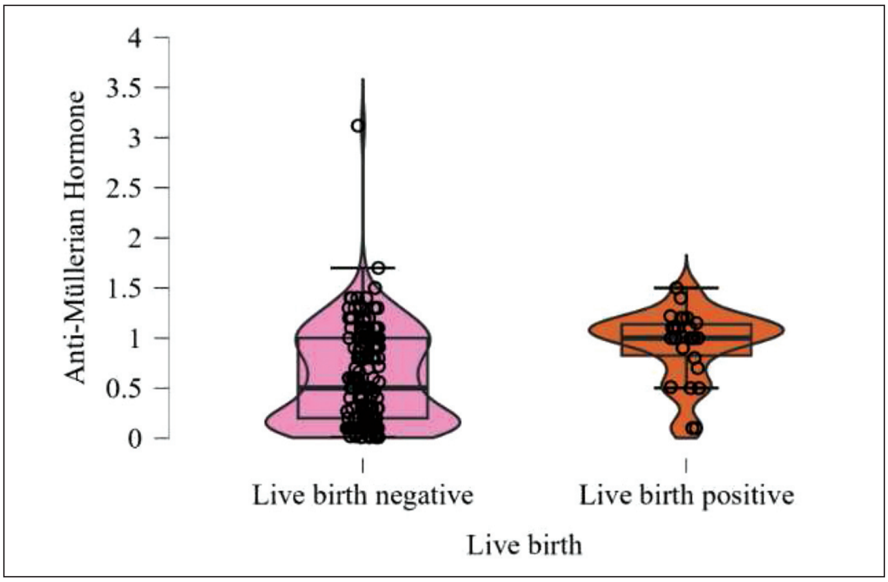

FIGURE 1: Violin plot of AMH distribution between live birth positive and negative groups

proportion of cases with two embryos transferred in the LB group was 50.0% compared to 30.2% in the non-LB group (p=0.048) (Table 1).

In univariate analysis, age (OR=0.92; p=0.048) and FSH level (OR=0.85; p=0.024) were significant predictors of LB, but lost significance in multivari-

TABLE 1: Clinical and laboratory parameters of patients with DOR undergoing IVF

Variables	Live Birth Positive Group (n=26)	Live Birth Negative Group (n=169)	p-value
Age(year)	33.46 ± 5.12	35.75 ± 5.43	**0.045***
BMI(kg/m^2)	24.48 ± 3.54	25.41 ± 3.14	0.167*
AFC(n)	5.39 ± 2.02	4.94 ± 2.20	0.328*
FSH(U/L)	7.96 ± 2.67	9.64 ± 3.56	**0.022***
LH(U/L)	7.57 ± 2.79	7.41 ± 3.27	0.817*
E2(ng/L)	41.02 ± 13.70	46.37 ± 18.28	0.154*
Total Gonadotropin Dose(IU)	2856.73 ± 606.49	2869.44 ± 576.03	0.917*
AMH(ng/mL)	0.94 ± 0.35	0.61 ± 0.48	**0.001***
E2 on hCG day(ng/L)	1087.62 ± 252.23	935.89 ± 442.97	0.090*
Progesteron (mikrog/L)	0.84 ± 0.26	0.92 ± 0.50	0.393*
Endometrial Thickness on hCG Day(mm)	10.44 ± 2.27	10.30 ± 6.05	0.911*
Stimulation Duration(day)	9.89 ± 1.34	10.15 ± 1.84	0.475*
Total Oocyte Count(n)	4.92 ± 1.90	3.82 ± 2.24	**0.019***
Metaphase II Oocyte Count(n)	3.31 ± 1.49	2.53 ± 1.63	**0.023***
Total Embryo Count(n)	2.19 ± 0.98	1.59 ± 1.04	**0.006***
Endometrial Thickness on Transfer Day(mm)	11.47 ± 2.19	10.28 ± 2.32	**0.015***
FET(n)	10 (38.5%)	23 (13.6%)	**0.002****
Transferred Embryo (n=149)			
Single Embryo	13 (50.0%)	104 (69.8%)	**0.048****
Double Embryo	13 (50.0%)	45 (30.2%)	
Embryo Grade(n)	(n=39)	(n=194)	
Grade 1	16 (41.02%)	51 (26.28%)	**0.008****
Grade 2	20 (51.28%)	83 (42.78%)	
Grade 3	3 (7.70%)	60 (30.94%)	

*independent t test(mean±SD), ** Chi Square test(n%); DOR: diminished ovarian reserve, IVF: in vitro fertilization, BMI: body mass index, AFC: antral follicle cout, FSH: follicle stimulating hormone, LH: luteinizing hormone, E2: estradiol, AMH: antimullerian hormone ate analysis (p >0.05). In contrast, AMH level significantly influenced LB outcomes in both analyses (univariate OR=4.13; p=0.003; multivariate OR=4.01; p=0.012) (Figure 2). In univariate analysis, total number of oocytes collected (OR=1.21; p=0.024), number of M2 oocytes (OR=1.28; p=0.029), total number of embryos formed (OR=1.65; p=0.008), endometrial thickness on the day of embryo transfer (OR=1.24; p=0.018) and FET (OR=3.96; p=0.003) were significantly associated with LB. In multivariate analysis, FET (OR=4.33; p=0.008) and embryo quality (Grade 1-3: OR=10.8; p=0.045) remained significant predictors. Double embryo transfer had no significant effect on LB rates compared to single embryo transfer (p >0.05) (Table 2).

At a cut-off value of 0.93 ng/mL, AMH showed a sensitivity of 72.7% and specificity of 69.23%, with a positive predictive value of 93.85% and a negative predictive value of 27.69%. The AUC indicating the

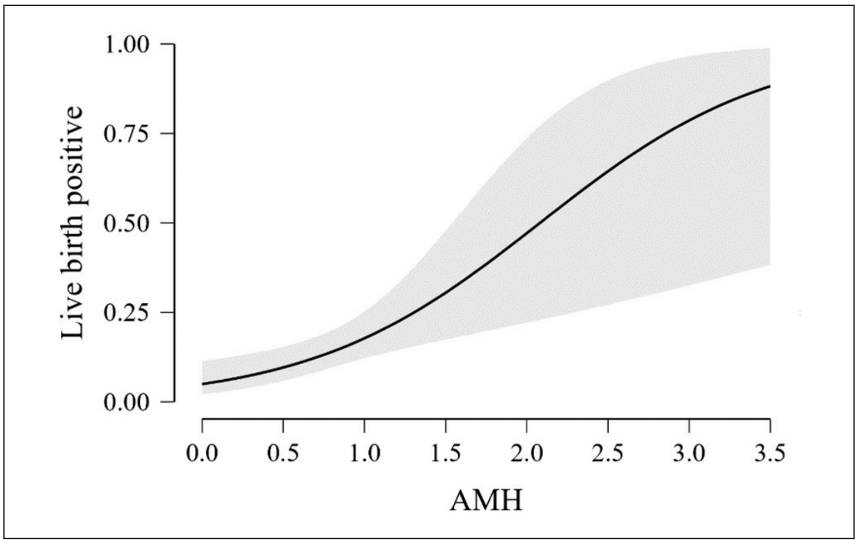

FIGURE 2: Curve plot of the relationship between anti-müllerian hormone level and live birth rate

TABLE 2: Univariate and multivariate regression analysis of factors affecting IVF outcomes in patients with DOR

	Univariate Analysis			Multivariate Analysis		
Projects	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age(year)	0.92	0.861-0.999	**0.048**	0.92	0.845-1.020	0.137
FSH(IU)	0.85	0.746-0.980	**0.024**	0.96	0.810-1.150	0.708
AMH(ng/mL)	4.13	1.63-10.427	**0.003**	4.01	1.357-11.90	**0.012**
Total collected oocyte(n)	1.21	1.025-1.438	**0.024**	1.34	0.882-2.060	0.167
M2 oocyte(n)	1.28	1.026-1.616	**0.029**	0.75	0.397-1.440	0.393
Total embryos formed(n)	1.65	1.139-2.405	**0.008**	0.85	0.402-1.840	0.695
ET on embryo transfer day(mm)	1.24	1.039-1.502	**0.018**	1.15	0.934-1.430	0.185
FET(n)	3.96	1.606-9.799	**0.003**	4.33	1.477-12.72	**0.008**
Double embryo transfer(n)	2.31	0.993-5.378	0.052	1.36	0.356-5.20	0.653
Embryo grade						
1-3	12.17	1.527-96.934	**0.018**	10.8	1.055-111.48	**0.045**
2-3	8.51	1.067-67.909	**0.043**	8.95	0.920- 87.19	0.059
1-2	1.42	0.597-3.416	0.422	1.21	0.445-3.293	0.708

ET: endometrial thickness, FET: frozen embryo transfer

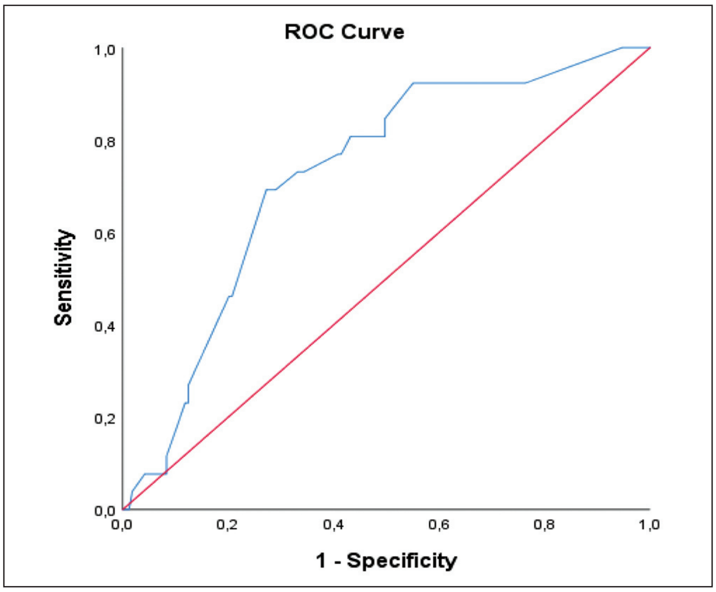

FIGURE 3: ROC curve of Anti-Müllerian Hormone in live birth prediction

TABLE 3: Performance of AMH in predicting live birth in diminished ovarian reserve

Variable	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)	p-value
Anti-Mullerian Hormone(ng/mL)	0.93	72.70	69.23	93.85	27.69	0.724(0.629-0.820)	0.001

predictive capacity of AMH was 0.724 (95% CI: 0.629-0.820), which was statistically significant (p = 0.001) (Figure 3, Table 3).

DISCUSSION

According to our study, AMH level is a strong predictor of LB, while other parameters offer more limited diagnostic accuracy. The cut-off value of 0.93 ng/mL for AMH level showed a significant association with LB rates.

AMH is a glycoprotein classified under the transforming growth factor beta family.[12] It is crucial for sex determination in early embryonic development. In females, it is produced by granulosa cells from mid-fetal life through adulthood, gradually decreasing during the reproductive years and significantly dropping at menopause, eventually becoming undetectable. AMH regulates follicular maturation by recruiting primordial follicles and is strongly linked to ovarian reserve, indicating a woman's ovulation potential.[13] AMH level is a dependable measure that mirrors the follicle reserve during the gonadotropin-independent stage and the count of ovarian follicles.[14]

Reshef Tal et al., analyzed 34,540 autologous IVF cycles of women with DOR, defined by AMH levels <1 ng/mL. The results showed that AMH levels are significantly correlated with cumulative live birth rate (CLBR), with a Pearson's correlation coefficient of 0.984 (p <00001). The same as our study, this demonstrates that AMH provides valuable predictive power in assessing a woman's chances of a LB through IVF, especially in the younger population, where the effect of AMH on CLBR is stronger.[4] In a live birth prediction model developed by Xiaoyun Gong et al., for patients with expected poor ovarian response during IVF/ICSI cycles, classified by POSEIDON criteria. It analyzed data from 657 women, identifying factors like age, BMI, AMH levels, number of normally fertilized oocytes, and basal FSH as key predictors of LB outcomes. A nomogram based on these factors was created, with a high predictive accuracy (AUC of 0.820 for the training set and 0.879 for the validation set).[15] In a retrospective study investigating the influence of age and AMH levels on IVF outcomes, it was found that younger women, particularly those under 35, exhibited higher rates of clinical pregnancy and live births, compared to older participants. The analysis highlighted that age and low AMH levels were not necessarily predictive of poor IVF outcomes if other variables like the total number of oocytes retrieved were favorable. This suggests that while age and AMH are important factors, they do not solely determine the success of fertility treatments.[16] Contrary to these findings, studies are emphasizing, AMH levels are a weak predictor of pregnancy as an independent variable, even at best, and should not be used as a fertility test.[17,18] AMH may contribute to IVF success by positively correlating higher AMH levels with an increased number of available embryos. A retrospective cohort study assessed the link between serum AMH levels and the quantity of viable embryos in IVF cycles for patients with poor ovarian reserves (POSEIDON Groups 3 and 4), the study confirmed that higher AMH levels correlate with a greater number of embryos.[19] In line with these findings, Tie-Cheng Sun et al., reported that elevated AMH levels are positively associated with an increased number of high-quality embryos and oocytes retrieved.[20] Thus, the high pregnancy rates may be attributed to the greater number of available embryos, as well as the retrieval of good-quality embryos and oocytes.

In another study age, BMI, AFC, and the type of controlled ovarian hyperstimulation (COH) protocol used were significant independent factors in predicting LB. A threshold effect analysis revealed an inflection point at age 34, after which the probability of LB declines sharply. BMI below 23.4 kg/m² was also associated with higher LB rates, while AFC above 8 increased the likelihood of LB.[21] However we did not find a significant positive effect of age and AFC on LB in both multivariate and univariate analysis. But, age was found to be lower in the LB positive group (33.46±5.12 years vs. 35.75±5.43 years, p=0.045). In addition, although not statistically significant, the number of antral follicles was higher in the LB-positive group (5.39±2.02 vs. 4.94±2.20) in our study.

Within the scope of our research endometrial thickness did not show a statistically significant effect on LB, in multivariate analysis. Similar to our study, Ata et al., examined 560 ET cycles, concluded that endometrial thickness does not predict LB rates, suggesting that women with thinner endometrium should not be excluded from embryo transfer opportunities, as their success rates are comparable to those with thicker endometrium.[22] Unlike ours, this study included 576 fresh and frozen embryo transfer cycles, independent of the indication for IVF, not just DOR. Hong Lv et al., discovered that as endometrial thickness increased, the LB rate also rose, leveling off once the thickness reached 11 mm or more. LB rate did not increase significantly with thicker endometrium.[23] We find 12 mm cut-off value for endometrial thickness, for LB. A recent comprehensive analysis from the Canadian Assisted Reproductive Technology Registry Plus database, categorizing cycles based on 2-millimeter variations in endometrial thickness, revealed that in fresh cycles, LB rates significantly rose up to an endometrial thickness of 10-12 mm. However, In FET cycles, LB rates leveled off at an endometrial thickness of 7-10 mm.[24] In short, the data are grouped broadly by endometrial thickness, which complicates determining the optimal cut-off for endometrial thickness that would lead to the best pregnancy outcomes.

In our study FET cycles were significantly associated with LB in multivariate analysis (OR=4.33, 95% CI: 1.477-12.72, p=0.008). A study exploring the efficacy of FET versus fresh embryo transfer in women above the age of 35 undergoing ICSI. A total of 513 embryo transfer cycles were analyzed, comprising 397 fresh embryo transfer and 116 FET cycles. The results demonstrated that FET cycles were associated with significantly higher biochemical pregnancy rates (43% vs. 32%, p=0.048), clinical pregnancy rates (38% vs. 29%, p=0.030), and live birth rates (30% vs. 19.6%, p=0.013) in comparison to fresh embryo transfer cycles. These findings suggest that FET may provide improved pregnancy outcomes and could be considered a more effective approach in women of advanced maternal age.[25] On the contrary, Yao Chen et. al, analyzes pregnancy outcomes in women of advanced maternal age who underwent either FET or fresh embryo transfer. FET group had gerater birth weights and reduced preterm birth rates compared to the fresh embryo transfer group. This study suggests that FET may reduce the risk of preterm birth, but may not necessarily improve LB rates for advanced maternal age women.[26] A study suggests FET may be beneficial in specific patient populations, particularly in high responders and PGT-A cycles, but not universally advantageous.[27] Aytek Sik et al., compared pregnancy outcomes in fresh embryo transfer and selective FET cycles in infertile patients aged 18-42. It found that selective FET resulted in higher clinical pregnancy and LB rates compared to fresh embryo transfer, suggesting that frozen transfers may be more effective in achieving successful pregnancies.[28] In our study, we also performed selective FET, applying total embryo freezing in patients with progesterone levels above 1 ng/dL. These findings, like our investigation, highlight the importance of applying FET in a selected patient population increases the chances of LB success.

The limitations of our study are primarily that it is retrospective and includes a small patient cohort size. An additional limitation is not separating the patients into fresh and frozen embryo transfer cycles.

CONCLUSION

AMH emerges as a crucial predictor of LB rates in patients with DOR, especially within the POSEIDON 3-4 groups. Although age and AFC hold importance, AMH levels offer the most substantial insight into the probability of LB. This underscores the advantage of tailored treatment approaches in ART, indicating that FET cycles might enhance LB outcomes for this specific group of patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Dilay Gök Korucu; **Design:** Dilay Gök Korucu; **Control/Supervision:** Dilay Gök Korucu; **Data Collection and/or Processing:** Orhan Kılınç; **Analysis and/or Interpretation:** Fatih Akkuş; **Literature Review:** Fatih Akkuş; **Writing the Article:** Dilay Gök Korucu; **Critical Review:** Şükran Doğru; **References and Fundings:** Oğuzhan Günenç; **Materials:** Dilay Gök Korucu.*

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