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Original Research

Evaluation of Clinical and Oocyte Morphological Parameters Associated With Fertilization Failure in Young Poor Ovarian Response Patients: A Retrospective Case-Control Study

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Abstract

Background: Infertility is a global healthcare problem affecting over 110 million women worldwide, with prevalence continuing to increase. Assisted reproductive technologies (ART) have contributed to improved treatment effectiveness. However, fertilization failure remains a significant concern among women with poor ovarian response. This study aimed to evaluate clinical, hormonal, and oocyte-related factors associated with fertilization failure in young patients with poor ovarian response (POR). **Methods:** We conducted a retrospective case-control study of 217 women <38 years of age meeting the criteria for POR, divided into two groups. This study was performed at an *in vitro* fertilization (IVF) center, Kayseri System Hospital, over a 2-year period (January 2022 to December 2023). Data were collected and analyzed using Statistical Package for the Social Sciences (SPSS). Continuous variables (age, body mass index (BMI), hormone levels, and oocyte count) were expressed as mean ± standard deviation (SD) and were compared between groups using independent-samples *t*-tests. Categorical data (oocyte morphological abnormalities) were reported as frequencies and percentages and were compared using chi-square tests. All patients underwent intracytoplasmic sperm injection (ICSI) cycles. **Results:** The study found no significant differences in age, BMI, or baseline hormone levels between groups. However, women with fertilization failure had significantly lower levels of estradiol (E2) upon human chorionic gonadotropin (hCG) trigger (631.0 ± 582.6 vs. 798.9 ± 535.3 pg/mL, $p = 0.03$), fewer cumulus–oocyte complexes (2.1 ± 2.1 vs. 3.5 ± 2.1, $p < 0.001$), and fewer mature (metaphase II) oocytes (1.2 ± 0.5 vs. 2.3 ± 0.7, $p < 0.001$). Morphological analysis revealed that smooth endoplasmic reticulum (SER) clusters were more frequent in the fertilization failure group (21% vs. 5%, $p = 0.0003$). Multivariable logistic regression analysis demonstrated that lower anti-Müllerian hormone (AMH) levels, higher baseline follicle-stimulating hormone (FSH) levels, higher total gonadotropin dose, and longer infertility duration were independently associated with fertilization failure after adjustment for potential confounding factors. **Conclusions:** Fertilization failure was positively associated with lower E2 levels on the day of hCG trigger, reduced oocyte yield, and a greater prevalence of SER clusters. Among young POR patients, SER clusters may represent the most frequently observed oocyte morphological abnormality associated with fertilization failure.

Keywords: infertility; assisted reproductive technologies; *in vitro* fertilization; intracytoplasmic sperm injection; fertilization; estradiol; oocytes; smooth endoplasmic reticulum

1. Introduction

Infertility is a significant global health problem, currently affecting over 110 million women worldwide, with prevalence rates rising to approximately 22% over the past three decades [1]. It is a multifactorial disorder arising from a combination of many factors such as ovulatory dysfunction, fallopian tubes occlusion, endometrial pathology, hormonal dysregulation, genetic abnormalities, and other undetermined causes [2]. Assisted reproductive technologies (ART) encompass a range of medical interventions that have transformed reproductive healthcare, offering viable pathways to parenthood when natural conception is not possible. During the decades since the first successful *in vitro* fertilization (IVF) birth in 1978, ART has evolved from experimental interventions into established clinical strategies that reliably enhance reproductive outcomes [3]. ART is primarily founded on IVF and intracytoplasmic sperm injection (ICSI). IVF enables fertilization to occur outside the body, while ICSI has revolutionized the management of severe male factor infertility by facilitating fertilization through the direct injection of a single sperm into the oocyte [4]. Several periodic innovations, including personalized ovarian stimulation protocols, preimplantation genetic testing, and advances in cryopreservation, have contributed to improved success rates and broader access to ART [5]. Apart from the direct effects of biological barriers to conception, ART also plays a crucial role in reducing the psychological and social burden of infertility, underscoring the need for transformative reproductive care systems worldwide [6]. However, fertilization failure remains one of the most challenging clinical outcomes, particularly in cases of recurrent failure or severely fragmented sperm DNA [7].

Procedures such as ICSI and its variants (e.g., Intracytoplasmic Morphologically Selected Sperm Injection (IMSI), artificial intelligence (AI)-guided ICSI), provide valuable evidence for addressing fertilization failure and continue to shape the field of reproductive medicine worldwide. IMSI and AI-guided ICSI aim at preventing such fertilization failure by optimizing sperm selection. Additional novel technologies, such as AI-assisted robotic ICSI, seek to minimize human error, improve procedural precision, and increase the overall effectiveness of ART [8]. Poor ovarian response (POR), as identified by the European Society of Human Reproduction and Embryology (ESHRE), is a central limitation of ART and is characterized by the retrieval of <4 oocytes following ovarian stimulation [9]. POR heterogeneity complicates both its identification and clinical management [10]. Advanced maternal age is frequently associated with reduced ovarian reserve and oocyte quality, and suboptimal outcomes may also be linked to male factor parameters [11]. This presents unique clinical challenges in a cohort of younger POR patients, in whom age-related decline cannot be ascribed to poor response, and the underlying causes of fertilization failure remain poorly understood [12]. Thus, personalized diagnostic and therapeutic approaches are required to optimize outcomes in this population [13]. In addition, female age correlates significantly with ART outcomes and ovarian reserve. Ovarian reserve declines progressively with age, particularly after 35 years, and this decline directly affects ovarian response and fertilization rates [14]. Clinically, ovarian reserve is assessed using transvaginal ultrasound measurement of antral follicle count (AFC) and serum biomarkers such as anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) [15].

Previous systematic reviews support the interpretation of ovarian response predictors and their association with IVF prognosis [16,17]. Body mass index (BMI) may also affect fertility and ovarian reserve. Several studies report that obese women exhibit lower AMH levels, reduced AFC, and poorer ovarian performance compared to normal-weight women [18,19,20,21]. According to IVF cohort meta-analyses, obesity is associated with a decrease in oocyte yield and an increase in miscarriage risk [22,23]. These outcomes are likely mediated by insulin resistance and chronic low-grade inflammation. Stimulation parameters like gonadotropin dose and duration of stimulation, influence ovarian response, E2 production, and oocyte yield, and thereby influence fertilization outcomes [24]. Oocyte quality is a crucial determinant of successful fertilization and subsequent embryo development. Morphological traits such as cytoplasmic appearance, polar body shape, perivitelline space, and smooth endoplasmic reticulum (SER) clusters are considered potential surrogate indicators of oocyte developmental competence. Abnormalities in these characteristics have been associated with significantly compromised fertilization rates and reduced embryo quality [25]. Cytoplasmic dysmorphisms, such as granularity or vacuolization, may serve as clinical indicators of diminished oocyte competence, while polar body or perivitelline space abnormalities may reflect disrupted maturation. Fertilization failure remains a major barrier to successful ART, particularly in patients with POR. Although advanced maternal age and male factor infertility account for the majority of fertilization failures, young POR patients with unexplained fertilization failure represent an understudied population. Despite previous work into the association between the clinical and oocyte morphological parameters (e.g., age, BMI, AMH, FSH, E2, and stimulation variables), evidence specific for this subgroup remains limited. To fill this gap, the current study aimed to assess the clinical and oocyte morphological parameters associated with fertilization failure in young POR patients without severe male factor infertility to improve prognostic accuracy and contribute to personalized treatment plans.

2. Materials and Methods

2.1 Study Design and Setting

This retrospective case–control study was conducted at the Kayseri System Hospital IVF Center in Kayseri, Türkiye, in collaboration with the Department of Obstetrics and Gynecology, Niğde Ömer Halisdemir University Training and Research Hospital. The study protocol was reviewed and approved by the Ethics Committee of Niğde Ömer Halisdemir University (Approval No.: 2025/07-109; Date: 06/05/2025). The study was conducted over a 2-year period from January 2022 to December 2023. The key aim was to examine the clinical and morphologic parameters associated with fertilization failure in young women with POR. Morphological examination of oocytes was performed by certified clinical embryologists in an inverted light microscope at standard ICSI magnification. Morphological scoring was performed prospectively at the time of oocyte retrieval, prior to determination of fertilization outcomes. Incomplete morphological records were excluded from the analysis.

2.2 Study Population and Sample Size

A total of 219 women aged <38 years with a diagnosis of POR were included. Of these, 87 women with total fertilization failure (TFF) were assigned to the case group (Group 1), and 132 women with successful fertilization were assigned to the control group (Group 2). However, 2 patients in the case group were subsequently excluded due to incomplete follow-up data, resulting in a final case group of 85 patients for analysis.

2.3 Data Collection

To obtain demographic and clinical information, clinical patient records included age, BMI, infertility duration, previous ART cycles, and baseline hormone status (AMH, Day-2 FSH, and E2). Further parameters measured were

Table 1. Comparison of oocyte morphological characteristics between the fertilization failure group and the control group.

Oocyte morphology feature	Fertilization failure group	Controls with fertilization	*p*-value
Dark cytoplasm or severe cytoplasmic granulation	111/407 (27%)	33/187 (18%)	0.0170
SER clusters	18/85 (21%)	7/132 (5%)	0.0003
Oval-shaped oocytes	12/407 (3%)	2/187 (1%)	0.1370
Large polar body	7/347 (2%)	1/186 (1%)	0.3800
Increased perivitelline space	161/347 (46%)	104/186 (56%)	0.0270

SER, smooth endoplasmic reticulum.

Table 2. Comparison of clinical and hormonal characteristics between the fertilization failure group and the control group.

Variable	Fertilization failure group (n = 85)	Controls with fertilization (n = 132)	*p*-value
Age (years)	33.2 ± 3.4	32.8 ± 3.4	0.320
BMI (kg/m^2)	24.6 ± 3.9	23.6 ± 4.4	0.080
Duration of infertility (years)	4.8 ± 4.2	4.0 ± 3.0	0.130
Day-2 FSH (IU/L)	10.4 ± 4.1	9.4 ± 3.0	0.090
Day-2 E2 (pg/mL)	46.6 ± 32.1	51.6 ± 32.2	0.340
AMH (ng/mL)	0.78 ± 0.9	0.99 ± 1.2	0.340
LH on hCG day (IU/L)	4.6 ± 4.0	3.8 ± 3.1	0.150
E2 on hCG day (pg/mL)	631.0 ± 582.6	798.9 ± 535.3	0.030*
No. of COCs	2.1 ± 2.1	3.5 ± 2.1	<0.001*
No. of MII oocytes	1.2 ± 0.5	2.3 ± 0.7	<0.001*
Total dose of gonadotropins used (IU)	2027.9 ± 1573.4	1852.8 ± 1180.5	0.350
Duration of stimulation (days)	7.3 ± 2.9	7.5 ± 2.1	0.580

Data presented as mean ± SD. Statistically significant values ($p < 0.05$) are indicated with an asterisk. BMI, body mass index; COCs, cumulus–oocyte complexes; MII, Metaphase II; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; E2, estradiol; LH, luteinizing hormone; SD, standard deviation; hCG, human chorionic gonadotropin.

gonadotropin injection dose, duration of stimulation, and hormone levels (LH and E2) on the day of human chorionic gonadotropin (hCG) trigger. Oocyte-related measurements included the number of cumulus–oocyte complexes (COCs) retrieved, number of mature (metaphase II, MII) oocytes, and specific oocyte morphology. Morphological assessment encompassed cytoplasmic abnormalities (granularity, vacuolization, dark cytoplasm), abnormal polar body, perivitelline space alterations, zona pellucida shape irregularities, and SER clusters. For the oocyte morphology analysis (Table 1), all mature (MII) oocytes collected from all ICSI cycles performed for each patient were included. However, COC and MII counts (Table 2) reflect index cycle values only, which were used for group classification.

2.4 Inclusion Criteria

Inclusion criteria were as follows: age <38 years; a diagnosis of POR based on the retrieval of fewer than four oocytes per the ESHRE; completion of controlled ovarian stimulation followed by ICSI cycles; and availability of clinical, biochemical, and morphological data.

2.5 Exclusion Criteria

Exclusion criteria were as follows: age ≥38 years; severe male factor infertility (sperm concentration <5 × 10^6/mL); diagnosis of endometriosis, polycystic ovary syndrome (PCOS), or uterine abnormalities that are confirmed to impact ART outcomes; and incomplete medical and/or laboratory records.

The patient selection process, exclusion criteria, and final study population are summarized in the patient flow diagram presented in Fig. 1.

2.6 Statistical Analysis

Data were analysed with Statistical Package for the Social Sciences (SPSS) (Version 25.0, IBM Corp., Armonk, NY, USA). Continuous variables (e.g., age, BMI, hormone count, number of oocytes) were expressed as mean ± standard deviation (SD), and group comparisons with independent samples *t*-test. Categorical variables (e.g., oocyte morphological abnormalities) were reported as frequencies and percentages, and between-group differences were assessed using chi-square tests. As this is an exploratory analysis, *p*-values were reported without adjustment for multiple comparisons. Statistical significance was defined as $p < 0.05$. Given that sample sizes exceeded 30 per group, approximate normality of the sampling distribution was assumed based on the Central Limit Theorem, regardless of the underlying population distribution [26]. However, in the current study, the case and control groups comprised 85 and 132 patients, respectively, both exceeding this threshold. Thus, the use of independent-samples *t*-test was considered valid, even for variables with biased data like oocyte counts and E2 values. Furthermore, chi-square tests were

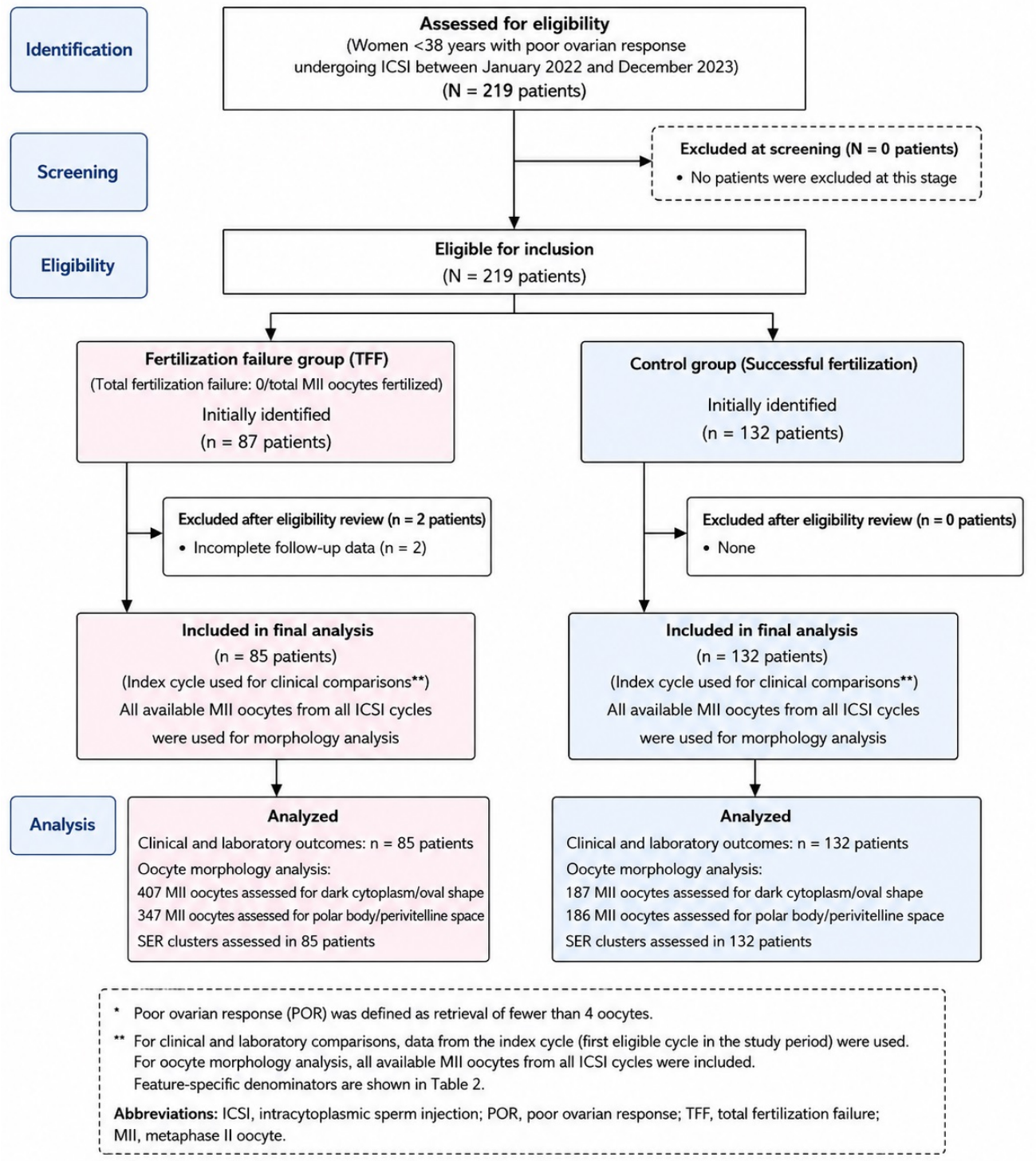

Fig. 1. Patient selection flow chart.

performed for categorical analyses. Morphological abnormalities were analyzed at the patient level rather than the individual oocyte level in order to minimize within-patient clustering effects. Between-groups comparisons of categorical variables were therefore performed using patient-based frequencies, with chi-square or Fisher's exact tests applied as appropriate.

3. Results

3.1 Clinical and Hormonal Characteristics of the Fertilization and Control Groups

Baseline and clinical characteristics between the fertilization failure group (n = 85) and the control group (n = 132) are shown in Table 2. Age, BMI, infertility duration, and hormone-level comparison (Day-2 FSH, AMH, or LH on hCG day) were not significant. In contrast, E2 levels

on the day of hCG trigger were significantly lower in the fertilization failure group compared with the control group ($p = 0.03$). Additionally, patients in the fertilization failure group exhibited significantly fewer COCs and MII oocytes retrieved compared to controls (both $p < 0.001$). These findings indicate that E2 levels and lower oocyte yield on the day of hCG trigger are significant clinical determinants of fertilization failure.

3.2 Morphological Characteristics of Oocytes and Association With Fertilization Failure

Morphological characteristics of retrieved oocytes are depicted in Table 1. A total of 407 MII oocytes from the fertilization failure group and 187 MII oocytes from the control group were analyzed. Oocytes from patients with fertilization failure showed a significantly higher incidence of SER clusters compared to controls (21% vs. 5%, $p = 0.0003$). For example, dark cytoplasm and severe cytoplasmic granulation were more frequent in this group (27% vs. 18%); the difference was statistically significant ($p = 0.017$). Other morphological parameters such as oval-shaped oocytes, abnormal polar bodies, and increased perivitelline space did not differ significantly between groups; however, increased perivitelline space was significantly different between groups ($p = 0.027$). Collectively, these results suggest that fertilization failure in young POR patients may be associated not only with reduced oocyte yield, but also with small morphological abnormalities, specifically the presence of SER clusters.

A multivariable logistic regression analysis was performed to identify factors independently associated with fertilization failure. Variables entered into the model included age, BMI, AMH, baseline FSH, gonadotropin dose, stimulation duration, and infertility duration.

After adjustment, lower AMH levels (odds ratio (OR) 0.58, 95% confidence interval (CI) 0.40–0.82, $p = 0.002$), higher baseline FSH levels (OR 1.13, 95% CI 1.03–1.23, $p = 0.012$), higher gonadotropin dose (OR 1.0005, 95% CI 1.0002–1.0007, $p < 0.001$), and longer duration of infertility (OR 1.15, 95% CI 1.04–1.26, $p = 0.004$) were independently associated with fertilization failure. Age, BMI, and duration of stimulation were not statistically significant in the adjusted model.

4. Discussion

Young patients with POR represent the focus of this study; however, fertilization failure is not exclusively age-related and remains a key barrier to ART success across broader patient populations. Identifying reliable predictors of fertilization outcomes in such patients is therefore of considerable clinical importance. In this study, patients with fertilization failure exhibited significantly lower levels of E2 on the day of hCG administration, as well as a reduced number of retrieved COCs and MII oocytes compared with controls. Notably, all participants underwent ICSI. TFF following ICSI is uncommon and may result from oocyte activation defects or subtle oocyte abnormalities. In conventional IVF, fertilization failure is commonly attributable to defects in sperm binding or penetration, which reflect sperm-oocyte interaction failures. Thus, this study was limited to ICSI cycles. Morphological analysis of oocytes revealed a higher frequency of SER clusters in the fertilization failure group compared to controls. Taken together, these suggest that both quantitative parameters (i.e., COC and MII counts) and qualitative parameters (i.e., SER clusters) are significantly associated with fertilization outcomes in young patients with POR. Nichi et al. (2011) [27] developed a predictive model for clinical pregnancy failure in POR patients undergoing IVF/ICSI, identifying maternal age >35 years, BMI >24, high baseline FSH levels >10 IU/L, and retrieval of <2 good quality embryos as major predictors. This model demonstrated a high predictive accuracy, with area under the curve (AUC) values of 0.786 in training and 0.748 in the validation cohort. Evidence from studies of young poor responders suggests that reduced Day-2 FSH levels, increased AMH levels, and sufficient MII oocyte yield are associated with improved fertilization rates, independent of E2 levels. Conversely, low E2 on the day of hCG trigger and a low MII oocyte count have been correlated with an increased risk of fertilization failure [27]. The findings of the current study are in agreement with the findings of patients in fertilization failure who have lower levels of E2, reduced COC and MII yields, and a higher frequency of SER clusters. Similarly, Schachter-Safrai et al. (2021) [28] also studied the association between ovarian reserve, oocyte quality, and the fertilization rates among women under 38 years of age undergoing IVF treatment. These studies showed that women with reduced ovarian reserve (DOR) produced significantly fewer COCs (4.2 vs. 9.1) and MII oocytes (2.8 vs. 7.5), and had a substantially higher fertilization failure rate (38% vs. 12%), despite similar hormonal profiles. Data up to October 2023 suggest that conventional markers such as FSH may be insufficient to fully predict fertilization outcomes, highlighting the additional prognostic value of oocyte quantity [28]. This aligns closely with our research analysis, in which low COC and MII oocyte counts were strongly related to fertilization failure. Furthermore, Jiang et al. (2023) [29] examined the predictive power of clinical and oocyte morphological variables in young POR patients, reporting results from 19,539 first IVF cycles (2013–2021). Using Least Absolute Shrinkage and Selection Operator (LASSO) and Extreme Gradient Boosting (XGBoost) machine learning models, they achieved an AUC of approximately 0.70 for prediction of TFF, which occurred in 7.5% of cycles. Oocyte yield was identified as the strongest predictor, whereas semen parameters exhibited little predictive value [29]. Additionally, lower COC and MII oocyte counts were found to be significant predictors of fertilization failure, confirming that oocyte-related parameters are predictive. In a retro-

spective study, Lebovitz et al. (2022) [30] investigated 751 IVF/ICSI cycles in women with POR according to Bologna criteria, characterized by the retrieval of ≤3 oocytes. They reported that fertilization failure was closely correlated with reduced number of oocytes retrieved (1.53 vs. 2.14), lower fertilization rates, and fewer high-quality embryos. Significantly, older age and higher oocyte yield were identified as predictors of higher success [30]. These findings are consistent with those of the current study, whereby lower COC and MII oocyte counts were observed more frequently in younger POR patients with fertilization failure. Robin et al. (2021) [31] examined the effect of endometriosis on oocyte morphology in 596 women undergoing IVF/ICSI, analyzing more than 6000 mature oocytes. On analysis of the Average Oocyte Quality Index (AOQI) and the Metaphase II Oocyte Morphological Scoring System (MOMS), no significant morphological differences were identified between women with vs. without endometriosis. Nevertheless, patients with endometriosis had significantly fewer MII oocytes (6.8 vs. 8.2), embryos (2.5 vs. 3.4), and clinical pregnancies (12% vs. 20%). These data suggest that endometriosis predominantly affects oocyte quantity rather than quality [31]. This pattern is consistent with the findings of the current study, in which decreased MII counts and similar hormonal profiles were observed in patients with fertilization failure. These results were supported by Lee et al. (2022) [32], who evaluated ART outcomes in POR patients classified using the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) criteria in a cohort of 225 patients over 374 cycles. Compared with normal responders, POSEIDON-classified patients had significantly lower oocyte retrieval rates (15 vs. 2–5), fewer embryos (11 vs. 2–4), and significantly lower clinical pregnancy rates (47.6% vs. 22.6%, 22.1%, 16.7%, 4.8% across the four POSEIDON groups, respectively). Logistic regression analysis confirmed that the POSEIDON categories represent greater risk of non-pregnancy [32]. Our results confirm these findings, further supporting reduced oocyte yield as a reliable and clinical predictor of ART outcomes.

Limitations

Several limitations of this study warrant acknowledgment. First, the retrospective design introduces the potential for selection bias. Second, the modest sample size may have limited the statistical power of subgroup analysis. Third, assessment of oocyte morphology was also subjective and operator-dependent. All associations were adjusted and may be subject to residual or unmeasured confounding. This analysis showed that lower E2 levels, decreased oocyte yield, and morphology abnormalities such as SER clusters were associated with fertilization failure. Although SER clusters were more prevalent in the fertilization failure group, this finding was exploratory and requires confirmation in large cohorts accounting for clustering and multiple comparisons. Receiver Operating Characteristic (ROC) curve analysis was not conducted, as the study was exploratory in nature and was not powered to evaluate diagnostic threshold values. These variables should be investigated in future prospective studies before clinical application. In addition, data on the specific ovarian stimulation protocol used (antagonist vs. agonist) were not systematically recorded, representing an additional unmeasured confounder. Addressing these limitations in future studies could improve prognosis, reinforce patient counseling, and support personalized and effective fertility care.

5. Conclusions

In this exploratory retrospective case–control of young POR patients undergoing ICSI, fertilization failure was associated with lower trigger-day E2 levels, lower oocyte yield, and a higher prevalence of SER clusters. Patients with fertilization failure had lower E2 levels on the day of hCG trigger, fewer COCs retrieved, and fewer MII oocytes than controls. These findings suggest that clinical, hormonal, and oocyte morphological markers, particularly SER clusters, may contribute to identifying patients at increased risk of fertilization failure, thereby supporting improved ART outcome prediction, personalized patient counseling, and individualized management. However, the potential role of SER clusters as a morphological marker should be confirmed in larger prospective studies.

Abbreviations

AFC, antral follicle count; AMH, anti-müllerian hormone; AOQI, Average Oocyte Quality Index; ART, assisted reproductive technologies; AUC, area under the curve; BMI, body mass index; COCs, cumulus–oocyte complexes; DOR, diminished ovarian reserve; E2, estradiol; ESHRE, European Society of Human Reproduction and Embryology; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; ICSI, intracytoplasmic sperm injection; IMSI, intracytoplasmic morphologically selected sperm injection; IVF, *in vitro* fertilization; LH, luteinizing hormone; MII, metaphase II; MOMS, Metaphase II Oocyte Morphological Scoring System; PCOS, polycystic ovary syndrome; POR, poor ovarian response; POSEIDON, Patient-Oriented Strategies Encompassing Individualized Oocyte Number; SD, standard deviation; SER, smooth endoplasmic reticulum; SPSS, Statistical Package for the Social Sciences; TFF, total fertilization failure.

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

EK conceived and organized the study, performed statistical analyses, and drafted the manuscript. EK, GO collected the data and conducted additional methodological research. EK, GO wrote the main text and analyses of the paper, while reviewing and revising the manuscript. EK and GO conceived and supervised the study, and also reviewed and revised the manuscript. Both authors reviewed and approved the final version of the manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Ethics Committee of Niğde Ömer Halisdemir University (Approval No: 2025/07-109, Date: 06/05/2025), and all procedures were performed in accordance with Declaration of Helsinki. Since this was a retrospective study, the informed consent requirement was waived.

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Conflicts of Interest

The authors declare no conflicts of interest.

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