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Diminished ovarian reserve is associated with impaired oocyte morphology and reduced ART outcomes in women under 35 years: a prospective cohort study

Fatemeh Dehghanpour
1Research and Clinical Center for Infertility Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd;

Nooshin Hatamizadeh
1Research and Clinical Center for Infertility Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd;

Hossein Fallahzadeh
2Research Center of Prevention and Epidemiology of Non-Communicable Disease, Department of Biostatistics and Epidemiology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

Saeideh Dashti
dashtisaeideh54@gmail.com

1Research and Clinical Center for Infertility Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd;

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Abstract

Background:

Diminished ovarian reserve (DOR) is primarily associated with reduced oocyte yield; however, its impact on oocyte quality and reproductive outcomes in young women remains unclear. This study aimed to evaluate oocyte morphology and assisted reproductive technology (ART) outcomes in women under 35 years with DOR compared to those with normal ovarian reserve (NOR**).**

Methods:

In this prospective cohort study, 202 women under 35 years undergoing ART between July and November 2025 were included. Participants were classified into NOR (n = 100) and DOR (n = 102) groups based on serum anti-Müllerian hormone levels (AMH < 1.1 ng/mL for DOR). Oocyte morphology was assessed according to the Istanbul Consensus Update 2024, and all parameters were expressed as percentages of metaphase II (MII) oocytes. Fertilization rate, embryo quality, and clinical pregnancy outcomes were compared between groups.

Results:

Women with DOR had significantly fewer retrieved and mature oocytes ($p < 0.001$). The proportion of morphologically normal MII oocytes was significantly lower in the DOR group (52.3% vs. 78.4%, $p < 0.001$), while cytoplasmic abnormalities, including vacuoles and smooth endoplasmic reticulum clusters, and extracytoplasmic abnormalities such as enlarged perivitelline space and abnormal polar body were more frequent (all $p < 0.001$). Fertilization rate (54.2% vs. 87.8%, $p < 0.001$) and the proportion of high-quality embryos (42.1% vs. 65.4%, $p < 0.001$) were significantly reduced in the DOR group. Clinical pregnancy rate was also lower in DOR (27.7% vs. 45.0%, $p = 0.011$).

Conclusions:

DOR in young women is associated with both reduced oocyte quantity and impaired oocyte morphology, accompanied by poorer ART outcomes. These findings suggest that ovarian reserve may reflect intrinsic oocyte competence. Integrating ovarian reserve assessment with oocyte morphology evaluation may improve prognostic accuracy in ART.

Introduction

Female fertility is a dynamic and highly regulated biological process, influenced by a complex interplay of hormonal, cellular, and environmental factors. Among these, ovarian reserve and oocyte quality are critical determinants of reproductive potential, affecting both spontaneous conception and assisted

reproductive technologies (ART)(1). As ART becomes a cornerstone of infertility treatment worldwide, identifying reliable predictors of ovarian response, oocyte competence, embryo formation, and pregnancy outcomes has become clinically essential(2).

One of the major challenges in reproductive medicine is diminished ovarian reserve (DOR), a condition that impairs both the quantity and potential quality of oocytes. Ovarian reserve reflects the functional capacity of the ovary and is primarily assessed using serum anti-Müllerian hormone (AMH) levels. A threshold of AMH < 1.1 ng/mL is a widely accepted indicator of DOR, incorporated into diagnostic frameworks such as the Bologna criteria and the POSEIDON classification(3). In this study, this clinical criterion was applied to differentiate women with DOR from those with normal ovarian reserve (NOR). Women with DOR often align with POSEIDON groups 3 and 4, representing individuals with inherently low ovarian reserve, which presents significant challenges for achieving optimal outcomes during controlled ovarian stimulation.

Oocyte quality is another pivotal factor that directly impacts fertilization, embryo development, blastocyst formation, implantation, and pregnancy(4). Optimal oocyte competence depends on the synchronous progression of nuclear and cytoplasmic maturation, ensuring accurate chromosomal segregation and early embryogenesis. Morphological assessment of oocytes remains a practical, though not definitive, tool for evaluating developmental potential(5). The Istanbul Consensus Update 2024 provides detailed guidelines for assessing oocyte morphology, describing optimal oocytes as spherical cells with uniform zona pellucida, appropriate perivitelline space, intact first polar body, and homogenous translucent cytoplasm. Abnormalities such as cytoplasmic granularity, vacuoles, smooth endoplasmic reticulum clusters, refractile bodies, irregular zona pellucida, or enlarged perivitelline space may indicate compromised oocyte competence, though evidence for some features remains inconclusive(6).

Despite extensive research on DOR and oocyte quality, an important clinical paradox persists. While DOR is associated with reduced oocyte number and suboptimal ART outcomes, younger women with DOR may retain oocyte competence, as chronological age is a dominant predictor of oocyte euploidy and embryo viability(7). Studies in women under 35 suggest that although oocyte yield may be lower, the intrinsic developmental potential of MII oocytes may not be significantly impaired. This highlights a potential dissociation between oocyte quantity and quality in younger DOR patients. However, inconsistencies in the literature remain, with many studies failing to adequately control for age, ovarian biomarkers, stimulation protocols, or embryo culture conditions(4).

Understanding the effects of DOR on oocyte morphology and pregnancy outcomes in younger women is clinically meaningful. With fertility treatment increasingly sought at younger ages, a growing proportion of ART candidates present with unexpectedly low AMH despite being under 35. For these women, the clinical question extends beyond oocyte number to the competence of the oocytes in producing healthy embryos and sustaining pregnancy(8).

Embryo quality and clinical outcomes, including implantation rate, biochemical pregnancy, and clinical pregnancy, are closely linked to oocyte health. Morphological abnormalities in oocytes can affect fertilization, cleavage-stage development, blastocyst formation, and implantation potential. While some dysmorphisms may be associated with aneuploidy or reduced developmental competence, the Istanbul Consensus Update 2024 emphasizes that many markers require further validation and should be interpreted cautiously.

Given these considerations, assessing the relationship between ovarian reserve status and oocyte morphology in young women is critical for refining clinical decision-making, optimizing stimulation protocols, and improving patient counseling(9). The present study aims to fill this gap by directly comparing oocyte quality and pregnancy outcomes between women with DOR and NOR undergoing ART in a high-volume fertility center. By applying standardized assessment criteria, including Istanbul morphology guidelines, alongside validated ovarian reserve markers such as AMH, this study provides a comprehensive evaluation to inform individualized treatment strategies(10).

The findings are expected to have significant clinical implications. If younger women with DOR maintain reasonable oocyte and embryo quality, treatment approaches may shift toward conservative stimulation, early fertility counseling, or modified embryo selection strategies. Conversely, substantial differences between DOR and NOR patients may warrant more aggressive stimulation protocols, adjunctive therapies, or earlier consideration of oocyte/embryo cryopreservation.

Unlike previous studies, the present study focuses exclusively on young women under 35 years of age, thereby minimizing the confounding effect of chronological aging on oocyte competence. Furthermore, oocyte morphological parameters were expressed as percentages of metaphase II oocytes, allowing for a more accurate evaluation of intrinsic oocyte quality independent of oocyte yield. The application of the updated Istanbul Consensus 2024 criteria also provides a standardized and contemporary framework for morphological assessment.

Materials and Methods

This prospective cohort study was conducted at the Yazd Reproductive Sciences Institute, a tertiary referral center for assisted reproductive technologies affiliated with Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Women under 35 years scheduled for ART were consecutively enrolled between July and November 2025. The study protocol was approved by the institutional ethics committee, and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Women undergoing ART during the study period were screened for eligibility. Eligible participants were younger than 35 years at the initiation of ovarian stimulation and had a baseline assessment of serum anti-Müllerian hormone (AMH) level. Only cycles progressing to oocyte retrieval and embryological evaluation were included. Exclusion criteria were applied to minimize confounding factors affecting ovarian function and oocyte quality and included polycystic ovary syndrome, endocrine disorders, severe

male factor infertility, uterine abnormalities, known chromosomal abnormalities, and cycles canceled prior to oocyte retrieval.

Participants were classified according to ovarian reserve status, as summarized in Table 1. Diminished ovarian reserve was defined by an anti-Müllerian hormone level <1.1 ng/mL, whereas normal ovarian reserve was defined by an anti-Müllerian hormone level ≥1.1 ng/mL .This classification reflects widely accepted clinical thresholds used in reproductive endocrinology and ovarian research(11).

Table 1. Baseline demographic and hormonal characteristics of women with normal ovarian reserve (NOR) and diminished ovarian reserve (DOR).

Variable	NOR (n=100)	DOR (n=102)	p-value
Age (years), mean ± SD	28.98 ± 3.27	28.47 ± 3.71	0.302
Duration of infertility (years), mean ± SD	3.92 ± 2.27	4.30 ± 1.75	0.156
AMH (ng/mL), mean ± SD	3.28 ± 1.16	0.48 ± 0.19	<0.001

Abbreviations: NOR, normal ovarian reserve; DOR, diminished ovarian reserve; AMH, anti-Müllerian hormone; BMI, body mass index; SD, standard deviation.

Controlled ovarian stimulation was performed using a standardized gonadotropin-releasing hormone (GnRH) antagonist protocol. Stimulation was initiated on cycle day 2 or 3 using recombinant follicle-stimulating hormone (rFSH) or human menopausal gonadotropin (hMG) at individualized doses ranging from 150 to 300 IU per day. The GnRH antagonist was administered when the leading follicle reached a diameter of 13–14 mm. Follicular development was monitored by serial transvaginal ultrasonography, and final oocyte maturation was triggered with human chorionic gonadotropin (hCG) or a GnRH agonist when at least two follicles reached a diameter of 18 mm or greater. All embryo transfers were performed on day 2 following oocyte retrieval.

Oocyte retrieval was performed 34–36 hours after trigger administration via transvaginal ultrasound-guided follicular aspiration. Retrieved cumulus–oocyte complexes were immediately transferred to the embryology laboratory for denudation and assessment of oocyte maturity. Oocytes were classified as germinal vesicle, metaphase I, or metaphase II, and only metaphase II oocytes were selected for intracytoplasmic sperm injection.

Oocyte morphological assessment was conducted by a single experienced embryologist to ensure consistency. The evaluation was performed according to the Istanbul Consensus Update 2024 guidelines and under blinded conditions, where the embryologist was unaware of the participants' ovarian reserve status. Both extra-cytoplasmic and intra-cytoplasmic features were evaluated, including zona pellucida uniformity, perivitelline space morphology, polar body integrity, cytoplasmic homogeneity, and the presence of vacuoles, smooth endoplasmic reticulum clusters, refractile bodies, or central

granularity. Oocytes meeting all criteria for structural integrity were classified as morphologically normal(12).

Intracytoplasmic sperm injection was performed on all metaphase II oocytes. Fertilization was assessed 16–18 hours after injection based on the presence of two pronuclei. Embryos were cultured and evaluated on day 2. Embryo quality was graded using standard morphological criteria for cleavage-stage embryos(1).

Embryo transfer was performed under ultrasound guidance. Serum beta-human chorionic gonadotropin levels were measured 14 days after embryo transfer to assess biochemical pregnancy, and clinical pregnancy was confirmed by the presence of a gestational sac with fetal cardiac activity at 6–7 weeks of gestation. Implantation rate was calculated as the number of gestational sacs divided by the number of embryos transferred(12).

Statistical Analysis

Data distribution was assessed using the Shapiro–Wilk test to determine normality. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were expressed as number (percentage). For comparison of continuous variables between the normal ovarian reserve (NOR) and diminished ovarian reserve (DOR) groups, the independent samples t-test was used for normally distributed data. In cases where normality assumptions were not met, the Mann–Whitney U test was applied. Categorical variables, including fertilization rate, embryo quality, and pregnancy outcomes, were analyzed using the chi-square test or Fisher's exact test when appropriate. Cross-tabulation analysis was used to evaluate the association between ovarian reserve status and pregnancy outcomes. Effect sizes for continuous variables were calculated using Cohen's d to quantify the magnitude of differences between groups. For categorical outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using binary logistic regression or contingency table analysis. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using Statistica version 7.1 software (StatSoft Inc., Tulsa, OK, USA).

Results

A total of 202 women who met the inclusion criteria were included in the final analysis. According to the predefined AMH threshold, participants were stratified into the normal ovarian reserve (NOR, n=100) and diminished ovarian reserve (DOR, n=102) groups. The median number of retrieved oocytes was significantly lower in the DOR group compared to the NOR group [3 (IQR 1-5) vs. 11 (IQR 7-15), $p < 0.001$]. Consequently, the number of metaphase II (MII) oocytes available for injection was also significantly lower in the DOR group [2 (IQR 1-4) vs. 8 (IQR 5-12), $p < 0.001$].

Oocyte Morphological Quality

The morphological analysis of MII oocytes, assessed according to the Istanbul Consensus criteria and expressed as a percentage of total MII oocytes, revealed significant differences between the groups (Table 2). The proportion of oocytes classified as morphologically normal was significantly lower in the DOR group compared to the NOR group ($p < 0.001$). Concurrently, DOR oocytes exhibited a significantly higher prevalence of both cytoplasmic and extracytoplasmic abnormalities.
Cytoplasmic abnormalities, including vacuolization, and the presence of smooth endoplasmic reticulum (SER) clusters, were all significantly more frequent in the DOR group (all $p < 0.01$). Regarding extracytoplasmic features, abnormalities such as enlarged perivitelline space, fragmented or irregular first polar body, and irregularities in the zona pellucida were significantly more common in oocytes from the DOR group (all $p < 0.001$)(Table 2). Representative micrographs depicting the range of oocyte morphologies evaluated in this study are compiled in Figure 1.

Table 2. Morphological characteristics of metaphase II (MII) oocytes according to Istanbul Consensus Update 2024.

Parameter		NOR (%)	DOR (%)	p-value
	Morphologically normal MII oocytes	78.4 ± 12.1	52.3 ± 18.6	<0.001
Cytoplasmic abnormalities	**≥1 cytoplasmic abnormality**	15.2 ± 8.5	32.7 ± 15.9	<0.001
	Vacuoles	5.1 ± 4.3	18.9 ± 12.4	<0.001
	SER clusters	1.5 ± 2.1	8.3 ± 7.8	<0.001
extracytoplasmic features	**Enlarged perivitelline space**	7.2 ± 7.5	30.5 ± 20.1	<0.001
	Fragmented/irregular polar body	6.0 ± 6.8	24.2 ± 21.4	<0.001
	Irregular zona pellucida	3.3 ± 4.0	14.7 ± 15.2	<0.001

Values are percentage of MII oocytes, mean ± SD

Fertilization and embryo development

Fertilization and embryo development outcomes are summarized in Table 3. The DOR group exhibited significantly lower numbers of fertilized oocytes and total embryos compared with the NOR group. In addition, fertilization rates and the proportion of high-quality embryos were significantly reduced in women with diminished ovarian reserve, while the proportion of lower-grade embryos was higher.

Table 3. Fertilization and embryo quality outcomes.

Variable	NOR	DOR	p-value
MII oocytes (mean ± SD)	8.2 ± 3.5	2.1 ± 1.4	<0.001
Total MII oocytes (n)*	929	249	-
Fertilized oocytes (2PN), n	816	135	<0.001
Fertilization rate (%)	87.8%	54.2%	<0.001
High-quality embryos (%)	65.4%	42.1%	<0.001

Abbreviations: DOR, diminished ovarian reserve; NOR, normal ovarian reserve; MII, metaphase II; 2PN, two pronuclei; SD, standard deviation.

 Fertilization rate was defined as the number of two pronuclei (2PN) divided by the number of metaphase II (MII) oocytes.

 High-quality embryo formation was defined as the proportion of grade A and B embryos among the total number of embryos.

Data are presented as mean ± standard deviation (SD) or number (percentage), unless otherwise indicated.

A p-value < 0.05 was considered statistically significant.

*Data are presented per cycle unless otherwise specified. Total counts represent pooled oocytes.

Clinical outcomes

Clinical outcomes are presented in Table 4. Biochemical pregnancy (42.6% vs. 57.0%, OR: 2.14, 95% CI: 1.17-3.92, p = 0.041) and clinical pregnancy rates (27.7% vs. 45.0%, OR: 1.79, 95% CI: 1.01-3.18, p = 0.011) were both significantly lower in the DOR group compared with the NOR group. Despite the younger age of participants, diminished ovarian reserve was associated with poorer clinical outcomes following ART.

Table4. Clinical pregnancy outcomes

Variable	DOR	NOR	OR (95% CI)	P-value
Chemical pregnancy rate/transfer (%), n/n	42.6% (43/102)	57.0% (57/100)	1.79 1.01-3.18	0.011
Clinical pregnancy rate/transfer (%), n/n	27.7% (28.102)	45.0% (45.100)	2.14 1.17-3.92	0.041

Abbreviations: DOR, diminished ovarian reserve; NOR, normal ovarian reserve; ET, embryo transfer; OR, odds ratio; CI, confidence interval.

The values within parenthesis represent%.

*) Chi-square test; OR: odds ratio; CI: confidence interval,

A p-value < 0.05 was considered statistically significant.

Discussion

The present study provides a comprehensive evaluation of the impact of diminished ovarian reserve (DOR) on oocyte morphology and assisted reproductive technology (ART) outcomes in young women. By focusing on a population younger than 35 years of age and applying a standardized morphological assessment based on the Istanbul Consensus Update 2024, our findings isolate the effect of ovarian reserve from chronological aging and demonstrate that DOR is associated not only with a quantitative reduction in oocyte yield but also with a qualitative impairment in oocyte competence(13).

A key finding of this study is the significantly lower proportion of morphologically normal metaphase II (MII) oocytes in women with DOR compared with those with normal ovarian reserve. Importantly, all morphological parameters were calculated as percentages of MII oocytes, minimizing the confounding effect of reduced oocyte number and providing a more accurate assessment of intrinsic oocyte quality. This methodological approach strengthens the validity of our findings and aligns with current recommendations for oocyte morphology reporting(14).

Our results demonstrate a higher prevalence of cytoplasmic abnormalities, including granularity, vacuolization, and smooth endoplasmic reticulum (SER) clusters, in oocytes obtained from women with DOR(15). Cytoplasmic integrity is essential for proper organelle distribution, calcium homeostasis, and early embryonic development. The increased frequency of these abnormalities suggests compromised cytoplasmic maturation, which may reflect altered follicular microenvironment, mitochondrial dysfunction, and impaired metabolic support during folliculogenesis in women with reduced ovarian reserve. Previous studies have reported inconsistent associations between ovarian reserve markers and

oocyte morphology; however, many of those investigations did not control for age or used heterogeneous morphological definitions. By applying updated consensus criteria, our study provides clearer evidence linking diminished ovarian reserve to cytoplasmic dysmorphisms(16).

In addition to cytoplasmic alterations, extracytoplasmic abnormalities—including enlarged perivitelline space, abnormal first polar body morphology, and irregular zona pellucida—were significantly more common in the DOR group. These features are considered markers of meiotic and cytoskeletal disturbances and have been associated with reduced developmental competence. The higher frequency of abnormal polar bodies observed in our cohort may indicate defects in spindle formation or chromosome segregation, which are consistent with previous reports suggesting that reduced ovarian reserve may be accompanied by subtle meiotic instability even in younger women(17, 18).

The observed deterioration in oocyte morphology was paralleled by poorer fertilization and embryo development outcomes. Women with DOR exhibited significantly lower fertilization rates and a reduced proportion of high-quality embryos, supporting the concept that morphological abnormalities are not merely cosmetic findings but reflect underlying biological deficits affecting oocyte developmental potential. These findings reinforce the clinical relevance of detailed oocyte morphology assessment and underscore its value as an intermediate phenotype linking ovarian reserve status to ART success(19).

Importantly, the negative impact of diminished ovarian reserve extended to clinical outcomes. Despite comparable stimulation protocols and similar duration of ovarian stimulation, implantation and clinical pregnancy rates were significantly lower in the DOR group. This observation suggests that reduced oocyte competence, rather than differences in treatment intensity, is a major contributor to poorer reproductive outcomes in this population(20). The fact that these effects were evident in relatively young women highlights that ovarian reserve reflects more than reproductive lifespan and may serve as a surrogate marker for follicular and oocyte health.

The strengths of this study include its age-restricted design, standardized morphological evaluation based on the most recent consensus guidelines, and the calculation of morphology parameters relative to MII oocytes, which enhances interpretability and comparability. Nevertheless, certain limitations should be acknowledged .Although this was a prospective cohort study, certain limitations should be considered. The single-center design may introduce selection bias. Additionally, molecular or metabolic assessments of oocytes were not performed, which could further elucidate the biological mechanisms underlying the observed morphological changes(21).

From a clinical perspective, our findings have important implications. They suggest that counseling of young women with diminished ovarian reserve should address not only the expected reduction in oocyte number but also the potential compromise in oocyte quality. Furthermore, these results support the incorporation of detailed oocyte morphology assessment into routine ART evaluation and future research, particularly in populations traditionally considered to have favorable prognoses based on age alone(22).

One possible biological explanation for the observed morphological alterations in DOR oocytes is impaired mitochondrial function and altered follicular microenvironment. Reduced ovarian reserve has been associated with compromised granulosa cell function, oxidative stress, and disrupted metabolic support, all of which may adversely affect cytoplasmic maturation and organelle distribution. These mechanisms may underlie the increased prevalence of cytoplasmic abnormalities observed in the present study.

Future multicenter studies incorporating molecular and genetic markers of oocyte competence are warranted to validate and extend these findings.

Another limitation is the relatively short recruitment period and the absence of live birth outcome assessment.

Conclusion

In conclusion, diminished ovarian reserve in young women is associated with both quantitative and qualitative impairments in oocyte competence. Beyond the well-recognized reduction in oocyte yield, our findings demonstrate a significantly lower proportion of morphologically normal metaphase II oocytes and a higher prevalence of cytoplasmic and extracytoplasmic abnormalities in women with diminished ovarian reserve. These morphological alterations were accompanied by reduced fertilization efficiency, impaired embryo development, and lower implantation and clinical pregnancy rates. Collectively, these results underscore that ovarian reserve reflects not only the remaining follicular pool but also the biological integrity of oocytes. Assessment of ovarian reserve should therefore be integrated with detailed evaluation of oocyte quality to provide a more accurate prognosis in assisted reproductive technology.

Clinical Implications

The findings of this study have several important clinical implications for the management of young women undergoing assisted reproductive technology. First, counseling of patients with diminished ovarian reserve should extend beyond expectations of reduced oocyte number and address the potential for compromised oocyte quality and developmental competence. Second, detailed assessment of oocyte morphology, particularly when standardized according to updated consensus criteria, may offer valuable prognostic information and help refine individualized treatment strategies.

Third, these results highlight the need for cautious interpretation of chronological age as a sole predictor of reproductive potential, as diminished ovarian reserve may confer an unfavorable prognosis even in younger patients. Incorporating ovarian reserve markers together with oocyte morphological evaluation may improve patient stratification, optimize clinical decision-making, and support more realistic expectations regarding treatment outcomes. Finally, the observed association between diminished ovarian reserve and altered oocyte morphology emphasizes the importance of future research aimed at

elucidating the underlying biological mechanisms and developing targeted interventions to improve oocyte competence in this challenging patient population.

Declarations

Author Contributions

FD, NH, and SD contributed to the conception and design of the study. FD and SD were responsible for data collection, oocyte assessment, and embryological evaluation. HF performed the statistical analysis and contributed to data interpretation. SD supervised the study and ensured the overall scientific integrity of the project. FD and SD drafted the manuscript. NH contributed to critical revision of the manuscript. All authors reviewed and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

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

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Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Written informed consent was obtained from all participants prior to enrollment in the study. All procedures were performed in accordance with the Declaration of Helsinki (Approval No. IR.SSU.RSI.REC.1403.024).

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

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Figures

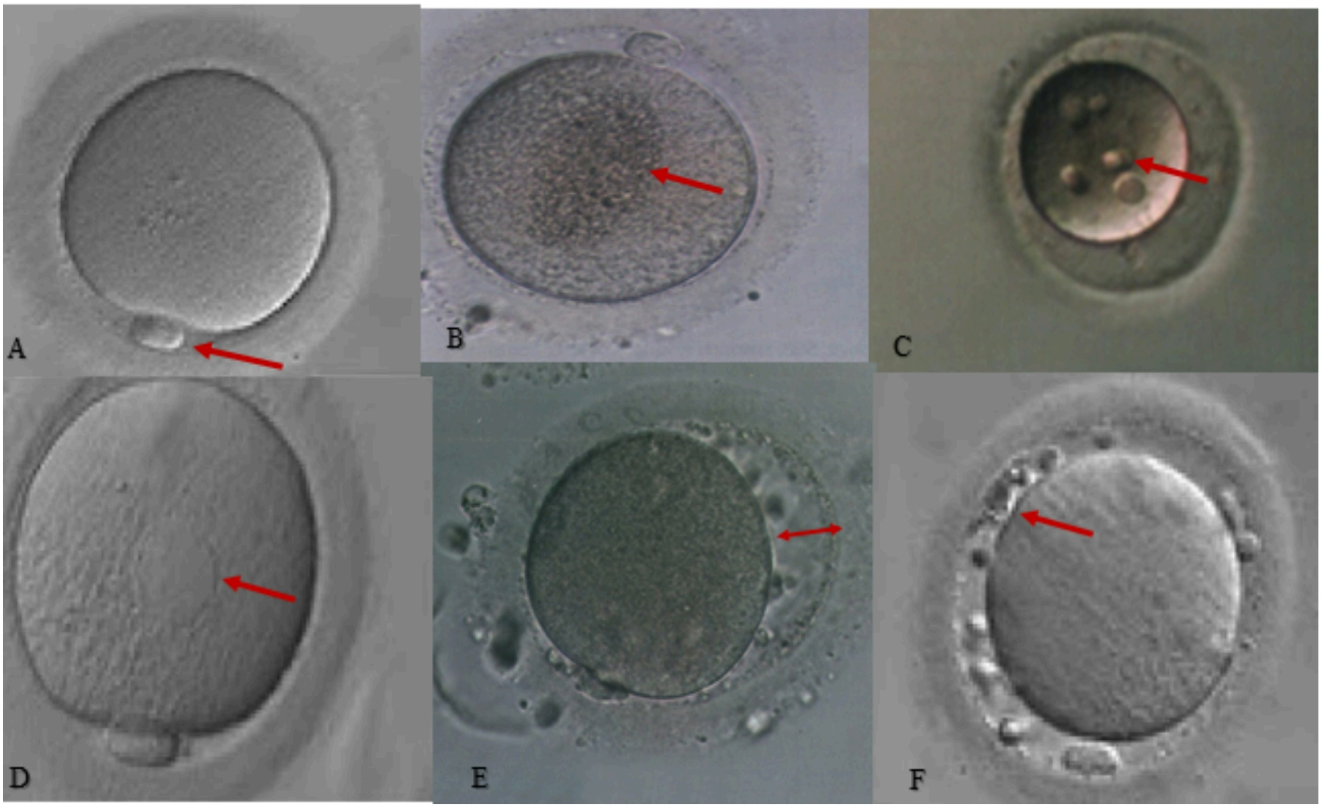


Figure 1

Representative morphological features of human metaphase II oocytes.

(A) Oocyte with optimal morphology: homogeneous cytoplasm, intact first polar body (arrow), regular zona pellucida, and normal perivitelline space.

(B) Cytoplasmic granularity (arrowhead).

(C) Multiple cytoplasmic vacuoles (arrowheads).

(D) Smooth endoplasmic reticulum cluster (asterisk).

(E) Enlarged perivitelline space (double-headed arrow).

(F) Fragmented first polar body (arrow).

Scale bar = 50 μm (applies to all panels). All images were obtained from oocytes assessed in this study using standard inverted microscopy (400× magnification).