Inverted microscopy as a high performance tool for pre denudation evaluation of oocyte nuclear maturity

Denüdasyon öncesi oosit nükleer matürasyonunun değerlendirilmesinde yüksek performanslı bir araç olarak invert mikroskopi

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Abstract

Objective: We aimed to show that inverted microscope is a reliable and highly accurate method for evaluating oocyte nuclear maturation before cumulus-oocyte complex (COC) denudation.

Materials and Methods: This single-center prospective observational study was conducted between 15 October and 15 November 2025. Non-dominant follicles with a diameter <10 mm were retrieved and evaluated under an inverted microscope to predict oocyte nuclear maturation prior to COC denudation. A total of 974 oocytes were retrieved from 59 patients; 250 COCs obtained from follicles <10 mm were analyzed. COCs were divided into three groups: (i) COCs with germinal vesicle (GV) oocytes, (ii) COCs with non-GV oocytes, and (iii) unclassified COCs. Two hours later, COCs were denuded, and the diagnostic accuracy of the inverted microscope was assessed.

Results: Ninety-seven COCs were classified as GV, 127 as non-GV, and 26 as unidentified. After denudation, 94 of 97 COCs were confirmed as GV oocytes, and 124 of 127 COCs were confirmed as non-GV oocytes. The accuracy of the inverted microscope in identifying nuclear maturation for GV and non-GV oocytes was 96.91% and 97.64%, respectively. No statistically significant difference in diagnostic accuracy was observed between embryologists.

Conclusion: Currently, no method can definitively determine oocyte nuclear maturation before COC denudation. This method allows the prediction of oocyte nuclear maturation before denudation with high accuracy, potentially improving in vitro maturation outcomes by preserving cumulus-oocyte communication.

Keywords: Nuclear maturation, inverted microscope, in vitro maturation, germinal vesicle, polar body

Öz

Amaç: Bu çalışmada, invert mikroskobun, kümülüs-oosit kompleksi (KOK) denüdasyonundan önce oosit nükleer matürasyonunu değerlendirmek için güvenilir bir yöntem olduğunu göstermeyi amaçladık.

Gereç ve Yöntemler: Bu tek merkezli prospektif gözlemsel çalışma,15 Ekim-15 Kasım 2025 tarihleri arasında gerçekleştirilmiştir. Çapı <10 mm olan foliküllerden elde edilen KOK'lar denüdasyondan önce oosit nükleer maturasyonunu tahmin etmek amacıyla invert mikroskop altında değerlendirilmiştir. Toplam 59 hastadan 974 oosit toplanmış, ve <10 mm foliküllerden elde edilen 250 KOK analiz edilmiştir. KOK'lar üç gruba ayrılmıştır: (i) germinal vezikül (GV) oosit içeren KOK'lar, (ii) GV olmayan oosit içeren KOK'lar ve (iii) sınıflandırılamayan KOK'lar. İki saat sonra, KOK'lar denüdasyona tabi tutulmuş ve invert mikroskobun tanısal doğruluğu değerlendirilmiştir.

PRECIS: Inverted microscope allows the prediction of oocyte nuclear maturation before denudation with high accuracy, potentially improving in vitro maturation outcomes by preserving cumulus-oocyte communication.

Bulgular: İnvert mikroskop ile değerlendirme sonrası 97 KOK GV oosit içeriyor, 127 KOK GV olmayan oosit içeriyor ve 26 KOK ise tanımlanamayan olarak sınıflandırıldı. Denüdasyondan sonra, 97 KOK'un 94'ü GV oosit, 127 KOK'un 124'ü ise GV olmayan oosit olarak doğrulandı. İnvert mikroskobun GV ve GV olmayan oositler için nükleer olgunlaşmayı belirlemedeki doğruluğu sırasıyla %96,91 ve %97,64 idi. Embriyologlar arasında tanı doğruluğunda istatistiksel olarak anlamlı bir fark gözlenmedi.

Sonuç: Günümüzde, KOK içindeki oositin nükleer matürasyonunu, KOK'u denüde etmeden önce belirleyebilecek bir yöntem bulunmamaktadır. Tanımladığımız bu yöntem ile denüdasyon öncesi oosit nükleer maturasyonu yüksek doğrulukla tahmin edilebilmektedir. Böylelikle KOK denüde edilmeden oosit nükleer matürasyonu belirlenebilecek ve in vitro olgunlaştırma sonuçları potansiyel olarak iyileştirilebilecektir.

Anahtar Kelimeler: Nükleer matürasyon, invert mikroskop, in vitro olgunlaştırma, germinal vezikül, polar body

Introduction

In vitro maturation (IVM) is a treatment modality nearly as old as in vitro fertilization (IVF) itself, first described by Pincus and Enzmann in 1935 and later defined by Edwards in 1962[1]. Classically, immature oocytes are collected and matured outside the body under laboratory conditions. Four main IVM protocols are described: (i) standard IVM, (ii) biphasic IVM, (iii) human chorionic gonadotropin (hCG)-primed IVM, and (iv) rescue IVM. In standard IVM, oocytes are retrieved after a short (2-3-day) stimulation period without an hCG trigger, and maturation is completed *in vitro* in one step[1]. In biphasic IVM, a pre-culture phase temporarily prevents meiosis to allow cytoplasmic maturation. In rescue IVM, germinal vesicle (GV) oocytes obtained after denudation in a conventional IVF cycle are matured *in vitro*. Rescue IVM is performed to obtain a higher number of metaphase-II oocytes, 2-pronuclear (2PN) zygotes and blastocysts, particularly in patients with diminished ovarian reserve (DOR), poor ovarian response (POR), or premature ovarian failure[2-4]. However, the success rate of rescue IVM has been reported as low because denudation disrupts the bidirectional interaction between oocytes and cumulus cells[3,4].

Currently, there is no definitive method for detecting oocyte nuclear maturation before denudation. Although several studies have attempted to estimate oocyte maturity by assessing cumulus-oocyte complex (COC) morphology under a microscope, these approaches have proven unreliable. Recently, Peker et al.[5] investigated the relationship between COC morphology and oocyte nuclear maturation and concluded that morphology alone is an unreliable indicator. The objective of this study was to present a new method that enables the highly accurate prediction of oocyte nuclear maturation prior to denudation.

Materials and Methods

We conducted a single-center prospective observational study between July 1 and September 1, 2025. The study was reviewed and approved by the Acıbadem University Ethics Committee and was performed in accordance with the principles of the 1975 Declaration of Helsinki, as revised in 2000 (approval no: 2025-14/541, date: 18.09.2025). Informed consent was obtained from all participants prior to inclusion.

On day 2 or 3 of the menstrual cycle, antral follicles were counted by transvaginal sonography. All patients received an antagonist protocol, and follicles were triggered using hCG, gonadotropin-releasing hormone agonist, or a combination of both. Oocyte retrieval was performed 36 hours after triggering, under sedation, using a 17-G needle.

Three embryologists participated in the study. Two embryologists, blinded to each other's evaluations, assessed oocytes using an inverted microscope, while a third embryologist, also blinded, performed denudation. During oocyte retrieval, dominant follicles and those larger than 10 mm were first aspirated and placed in a four-well dish. The remaining non-dominant follicles (<10 mm) were collected separately and examined under an inverted microscope by one of the two embryologists. First, follicular fluid was examined under a stereomicroscope to determine the presence of COCs. When COCs were detected, they were evaluated in a Petri dish using an inverted microscope. After assessment, the embryologists classified each COC into three groups: (i) COCs containing GV oocytes, (ii) COCs containing non-GV oocytes (including metaphase-I and metaphase-II oocytes), and (iii) COCs that could not be clearly identified as GV or non-GV. Two hours later, denudation was performed by the third embryologist and the accuracy of the inverted microscope evaluation was determined.

Evaluation of COCs Under Inverted Microscope

Follicular fluid was poured into a 90-mm Petri dish, which was then tilted at a 30-45 °C angle to spread and visualize the COCs. COCs were subsequently examined using the same dish under an inverted microscope to determine nuclear maturation. Immediately before observation, the cumulus was gently spread laterally with a pipette to improve visualization of the oocyte.

Under the inverted microscope, oocytes displaying a GV were recorded as GV oocytes, while those with a visible polar body were categorized as non-GV oocytes. Oocytes lacking both a GV and a polar body were designated as having undefined nuclear maturity. Figure 1 illustrates images of a GV (GV oocyte) and a polar body [metaphase II (MII) oocyte].

Statistical Analyses

All data obtained in the study were analyzed using SPSS (IBM SPSS Statistics version 2.5, Chicago, IL, USA). Data distributions are presented as medians and percentages. Normality was assessed using Kolmogorov-Smirnov tests (n>30). The chi-square test was applied to categorical

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variables, and the Mann-Whitney U test was applied to continuous variables. A 95% confidence level was adopted for all analyses.

Results

A total of 100 patients were initially enrolled in the study. In 41 patients, no COCs could be retrieved from follicles <10 mm; therefore, these patients were excluded. A total of 974 oocytes obtained from 59 patients were analyzed. Of these, 724 oocytes originated from follicles ≥10 mm, and 250 from follicles <10 mm were included as the study group.

Table 1 summarizes the success rate in identifying mature and immature oocytes using the inverted microscope. Among the 250 COCs evaluated, 97 were classified as GV oocytes. After denudation, 94 oocytes were confirmed as GV, 2 as MII, and 1 as metaphase I (MI). Of the 127 COCs classified as non-GV, 124 were confirmed as non-GV and three were GV after denudation (108 MII, 16 MI). Twenty-six COCs could not be classified and were designated as unidentified. The overall accuracy of the inverted microscope in detecting oocyte nuclear maturation was 96.91% for GV oocytes and 97.64% for non-GV oocytes.

Table 2 presents the performance of embryologist 1 in predicting oocyte nuclear maturation using the inverted microscope. A total of 120 COCs were assessed; 38 were classified as GV, 69 as non-GV, and 13 as unidentified (group 3). The success rate for detecting oocyte nuclear maturation was 97.10% for GV oocytes and 97.37% for non-GV oocytes. Table 3 presents the performance of embryologist 2. A total

of 130 COCs were evaluated; 59 were classified as GV, 58 as non-GV, and 13 as unidentified (group 3). The accuracy rates were 98.28% for GV and 96.91% for non-GV oocytes. No statistically significant difference was found between the two embryologists in diagnostic accuracy for GV versus non-GV classification.

The diagnostic performance of the imaging method was further compared using area under the curve (AUC) values. Figure 2 shows the receiver operating characteristic (ROC) curve for the inverted microscope. The ROC AUC was 0.99, indicating excellent predictive accuracy for oocyte nuclear maturation (R^2=0.989, mean absolute error=0.127, root mean square error=0.252).

Figure 3 shows the regression analysis results for the inverted microscope. The regression line corresponded closely with denudation scores, showing minimal deviations and a balanced distribution. These results demonstrate that measurements obtained with the inverted microscope show a strong linear correlation with oocyte nuclear maturation outcomes.

Table 1. Diagnostic accuracy of inverted microscopy in identifying GV and non-GV oocytes prior to denudation

	Mature (%)	Immature (%)	p-value
Embryologist 1	97.37	97.10	>0.05
Embryologist 2	96.61	98.28	>0.05
Total	96.91	97.64	

GV: Germinal vesicle

Figure 1. The upper-left image represents an oocyte (in metaphase 2) and was taken using an inverted microscope. Red arrow indicates a polar body (i.e., at 12 o'clock). The upper-right and the bottom-right photos show a GV as observed under an inverted microscope (red arrow). The bottom-left image depicts neither GV nor the polar body. Therefore, whether this image is a GV or MII oocyte remains uncertain
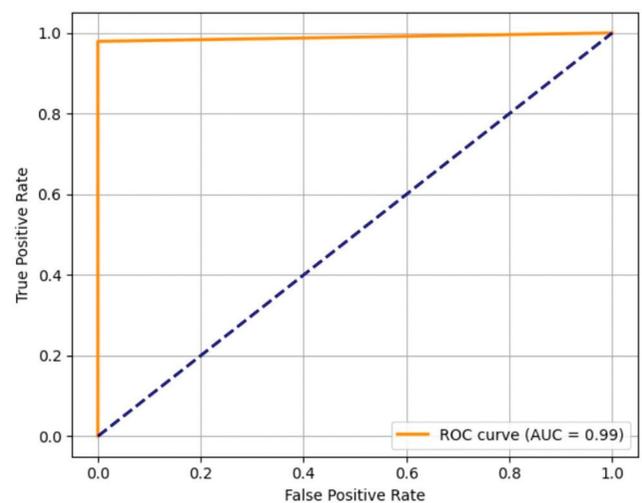
GV: Germinal vesicle, MII: Metaphase II

Figure 2. ROC curve, the new "inverted microscope" method has a very high success rate in predicting oocyte nuclear maturation before denudation. R^2=0.989, MAE=0.127, RMSE=0.252, ROC AUC=0.99

ROC: Receiver operating characteristic, RMSE: Root mean square error, AUC: Area under the curve, MAE: Mean absolute error
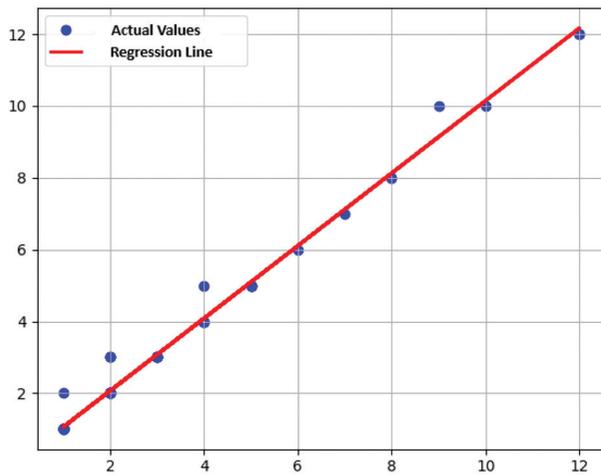
Figure 3. Regression analysis. The regression line matches the denudation score trend well. Deviation from a linear relationship is minimal and the distribution is balanced. Taken together, these data demonstrate that the inverted microscope is capable of reliably predicting oocyte nuclear maturation

Discussion

Rescue in vitro maturation (r-IVM) refers to the IVM of denuded, immature oocytes after triggering with hCG and/or a GnRH agonist during a conventional IVF cycle[6]. This approach can increase the number of mature oocytes obtained in a single cycle, particularly in patients with DOR, POR, or primary ovarian insufficiency. However, its effectiveness is limited because denudation disrupts the bidirectional communication between cumulus cells and the oocyte[6,7].

In a study by Qin et al.[4], the reproductive outcomes of rescue IVM were evaluated by comparing two groups: (i) 2112 women who underwent intracytoplasmic sperm injection (ICSI) and (ii) 490 women who underwent ICSI followed by rescue IVM. In the ICSI + r-IVM group, the number of MII oocytes, 2-pronuclear (2PN) embryos and day-3 embryos was higher than in the ICSI-only group. Similarly, Shani et al.[8] conducted a retrospective cohort study to assess the maturation potential of immature oocytes undergoing IVM, and reported that the fertilization rates of MI-rescue IVM and GV-rescue IVM oocytes were comparable to those of sibling MII oocytes. However,

Table 2. Diagnostic performance of embryologist 1 in predicting oocyte nuclear maturation under-inverted microscope

ID	COCs obtained from follicles <10 mm (n)	GV under inverted microscope (n)	GV after denudation (n)	Non-GV under inverted microscope (n)	Non-GV after denudation (n)	Unidentified cases under inverted microscope (n)	MII after denudation (n)	MI after denudation (n)	GV after denudation (n)
1	4	4	4	0	0	0	0	0	0
2	1	1	1	0	0	0	0	0	0
3	7	7	7	0	0	0	0	0	0
4	3	3	2	0	0	0	0	0	0
5	1	1	1	0	0	0	0	0	0
6	2	2	2	0	0	0	0	0	0
7	3	1	1	1	1	1	1	0	0
8	7	1	1	0	0	6	6	0	0
9	5	1	1	2	2	2	2	0	0
10	3	1	1	1	1	1	0	0	1
11	9	1	1	8	8	0	0	0	0
12	3	0	0	3	3	0	0	0	0
13	3	0	0	3	3	0	0	0	0
14	2	1	1	1	1	0	0	0	0
15	2	0	0	1	1	1	1	0	0
16	2	1	1	1	1	0	0	0	0
17	6	1	1	5	5	0	0	0	0
18	1	0	0	1	1	0	0	0	0
19	6	0	0	6	6	0	0	0	0
20	4	4	4	0	0	0	0	0	0

Table 2. Continued

ID	COCs obtained from follicles <10 mm (n)	GV under inverted microscope (n)	GV after denudation (n)	Non-GV under inverted microscope (n)	Non-GV after denudation (n)	Unidentified cases under inverted microscope (n)	MII after denudation (n)	MI after denudation (n)	GV after denudation (n)
21	2	2	2	0	0	0	0	0	0
22	1	1	1	0	0	0	0	0	0
23	2	0	0	2	2	0	0	0	0
24	1	0	0	1	1	0	0	0	0
25	3	2	2	1	1	0	0	0	0
26	1	0	0	1	1	0	0	0	0
27	4	0	0	2	2	2	0	1	1
28	1	0	0	1	1	0	0	0	0
29	12	0	0	12	12	0	0	0	0
30	6	1	1	5	4	0	0	0	0
31	12	2	2	10	9	0	0	0	0
32	1	0	0	1	1	0	0	0	0
Total	120	38	37	69	67	13	10	1	2

GV: Germinal vesicle, MII: Metaphase II, MI: Metaphase I, COC: Cumulus-oocyte complex

Table 3. Diagnostic performance of embryologist 2 in predicting GV and non-GV oocytes under inverted microscope

ID	COCs obtained from follicles <10 mm	GV under inverted microscope	GV after denudation	Non-GV under inverted microscope	Non-GV after denudation	Unidentified cases under inverted microscope	MII after denudation	MI after denudation	GV after denudation
1	2	1	1	1	1	0	0	0	0
2	5	4	4	1	1	0	0	0	0
3	3	1	1	2	2	0	0	0	0
4	5	3	3	2	2	0	0	0	0
5	1	1	1	0	0	0	0	0	0
6	15	12	12	3	3	0	0	0	0
7	5	4	4	1	1	0	0	0	0
8	2	1	1	1	1	0	0	0	0
9	7	5	5	2	2	0	0	0	0
10	2	0	0	2	2	0	0	0	0
11	3	3	2	0	0	0	0	0	0
12	9	1	1	8	8	0	0	0	0
13	9	2	1	4	4	3	0	2	1
14	1	1	1	0	0	0	0	0	0
15	5	2	2	3	3	0	0	0	0
16	1	1	1	0	0	0	0	0	0
17	4	0	0	2	2	2	1	0	1
18	3	0	0	3	3	0	0	0	0

Table 3. Continued

ID	COCs obtained from follicles <10 mm	GV under inverted microscope	GV after denudation	Non-GV under inverted microscope	Non-GV after denudation	Unidentified cases under inverted microscope	MII after denudation	MI after denudation	GV after denudation
19	12	2	2	10	10	0	0	0	0
20	12	5	5	2	2	5	4	0	1
21	2	1	1	1	1	0	0	0	0
22	3	0	0	1	1	2	0	1	1
23	1	1	1	0	0	0	0	0	0
24	3	1	1	2	2	0	0	0	0
25	5	2	2	2	2	1	1	0	0
26	6	3	3	3	2	0	0	0	0
27	4	2	2	2	2	0	0	0	0
Total	130	59	57	58	57	13	6	3	4

GV: Germinal vesicle, MII: Metaphase II, MI: Metaphase I, COC: Cumulus-oocyte complex

early cleavage and blastulation rates were significantly lower in r-IVM group. Despite this, the euploid blastocyst and good-quality blastocyst rates were comparable with MII siblings, suggesting that r-IVM may enhance transferable blastocyst yield and overall IVF success[8]. Conversely, Bartolacci et al.[9] published a meta-analysis demonstrating that fertilization, cleavage, blastulation, and clinical pregnancy rates were significantly lower for r-IVM oocytes than for sibling MII oocytes. Several studies have attributed these poorer outcomes to the loss of COC. Cumulus cells play a critical role in supporting oocyte growth, development, and maturation by secreting regulatory molecules such as cAMP and cGMP. They also produce metabolic energy and facilitate nutrient transport to the oocyte[10-12]. Preserving this communication is, therefore, essential. Accurate identification of GV oocytes before denudation allows IVM to proceed without disrupting these interactions, potentially improving maturation and fertilization rates.

Only a limited number of studies have investigated the identification of mature and immature oocytes before denudation. Batsry et al.[13] reported that experienced embryologists could identify 90% of mature and 72.7% of immature oocytes before denudation. Similarly, Peker et al.[5] found that embryologists correctly identified 69% of immature and 80% of mature oocytes based on COC morphology. Hammitt et al.[14] further assessed embryologists' ability to predict nuclear maturation and reported correct prediction rates of 74%, 64%, and 47% for three observers. Across these studies, the predictive accuracy for nuclear maturation did not exceed 90%, suggesting that COC morphology alone is insufficient for reliable classification.

In our study, we developed and validated a new method, using inverted microscopy, to assess oocyte nuclear maturation before denudation. After evaluation, 96.91% of immature oocytes and 97.64% of non-GV oocytes were correctly identified. We believe that determining oocyte nuclear maturation before COC denudation represents a potentially transformative step in IVF practice. GV oocytes detected under an inverted microscope can be left to mature *in vitro* with their cumulus cells intact, thereby maintaining bidirectional communication and improving maturation rates.

Conclusion

Inverted microscopy provides a highly accurate, non-invasive method for assessing oocyte nuclear maturation prior to COC denudation. This technique may improve IVM outcomes, particularly in patients with limited oocyte yield. Its integration into standard IVF workflows could preserve cumulus-oocyte interactions, thereby enhancing oocyte maturation, fertilization, embryo development, and pregnancy rates. Moreover, in classical and biphasic IVM protocols, COCs can be evaluated using inverted microscopy before denudation, allowing an extended IVM period for immature oocytes to achieve the MII stage. Future studies should be multicenter, prospective, and incorporate molecular markers of oocyte maturation.

Ethics

Ethics Committee Approval: The study was reviewed and approved by the Acıbadem University Ethics Committee and was performed in accordance with the principles of the 1975 Declaration of Helsinki, as revised in 2000 (approval no: 2025-14/541, date: 18.09.2025).

Informed Consent: Informed consent was obtained from all participants prior to inclusion.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: N.P., A.Y., Ö.K., E.T., Concept: N.P., B.T., Design: N.P., E.T., B.T., Data Collection or Processing: N.P., A.Y., Ö.K., E.T., B.E., İ.Ö.A., S.D., Analysis or Interpretation: N.P., A.Y., S.D., B.T., Literature Search: N.P., Writing: N.P., E.T., B.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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