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Prediction of oocyte maturity before denudation: Is the assessment of COC morphology a reliable option?

Denudasyon öncesi oosit matürasyonunu tahmin etmek için KOK morfolojisi değerlendirilmesi güvenilir bir seçenek midir?

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Abstract

Objective: We aimed to demonstrate the predictive value of morphological assessment of cumulus-oocyte complexes (COCs) prior to denudation in distinguishing mature and immature oocytes.

Materials and Methods: The study consisted of two stages. Five embriologists were enrolled to the first stage of the study and they divided COCs into two groups according to the morphologic features of the COS's: COCs with mature oocytes and COCs with immature oocytes. The process was overseen by one embryologist. Two hours later, COCs were denuded, and the maturity of oocytes was evaluated by another embryologist. The results were recorded. The first stage was terminated when each embryologist had evaluated a minimum of 100 COCs. In the second stage, three embryologists applied the procedure continuously for one more month. At the end of the study, the effects of continuous assessment on the prediction success were evaluated.

Results: Eighty patients were enrolled in the study, and a total of 1039 COCs were examined. In the first stage of the study, 69% of immature and 80% of mature oocytes were identified correctly by the embryologists. There was no significant difference among the embryologists in terms of success rates. In the second stage of the study, the success rates of immature oocyte prediction increased for all three embryologists. However, a statistically significant increase was observed for only one embryologist ($p<0.05$). However, the prediction rates of mature oocytes were comparable with the results of the first stage of the study. There was no significant relationship between the number of COCs and the prediction value.

Conclusion: Morphological assessment of COCs before denudation does not provide accurate results in identifying mature and immature oocytes.

Keywords: Oocyte, maturation, in vitro fertilization

Öz

Amaç: Olgun oositler ile olgun olmayan oositleri denudasyon öncesi ayırt edebilmek amacı ile, denüdasyon öncesi kümülüs-oosit komplekslerinin (KOK) morfolojik değerlendirmesinin öngörü değerini göstermeyi amaçladık.

Gereç ve Yöntemler: Çalışma iki aşamadan oluşmaktadır. İlk aşamaya beş embriyolog dahil edildi. Her bir embriyolog denudasyon öncesi, KOK'ları morfolojik özelliklerini göz önüne alarak KOK'ları, olgun ve olgun olmayan oosit içeren KOK'lar olarak iki gruba ayırdı. İşlem bir embriyolog tarafından denetlendi ve iki saat sonra KOK'lar başka bir embriyolog tarafından denude edildi, oositlerin olgun olup olmadıkları not edildi. İkinci aşamada, üç embriyolog işlemi bir ay süre ile kesintisiz olarak uyguladı. Çalışmanın sonunda, KOK morfolojisinin sürekli aynı kişiler tarafından değerlendirilmesinin olgun-olgun olmayan oositi tahmin başarısı üzerindeki etkileri değerlendirildi.

Bulgular: Çalışmaya 80 hasta dahil edildi ve toplam 1039 KOK incelendi. Çalışmanın birinci aşamasında embriyologlar tarafından immatür oositlerin %69'u, matür oositlerin ise %80'i doğru olarak tanımlandı. Embriyologlar arasında başarı oranları açısından anlamlı bir fark saptanmadı. Çalışmanın ikinci aşamasında, immatür oositleri tahmin etme başarı oranı üç embriyolog için de artarken, matür oositleri tahmin etme başarısında sadece bir embriyolog için anlamlı artış gözlendi ($p<0,05$). Diğer iki embriyolog için matür oositleri tahmin etme oranları çalışmanın birinci aşamasının sonuçlarıyla karşılaştırılabilir düzeydeydi. Tek seferde değerlendirilen KOK sayısı ile tahmin başarısı arasında istatistiksel olarak anlamlı bir ilişki saptanmadı.

PRECIS: Morphological assessment of cumulus-oocyte complexes before denudation does not provide definitive results about oocyte maturity.

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Sonuç: Denudasyon öncesi KOK'ların morfolojik değerlendirilmesi olgun ve olgun olmayan oositlerin belirlenmesinde her zaman doğru sonuçlar vermemektedir.

Anahtar Kelimeler: Oosit, maturasyon, in vitro fertilizasyon

Introduction

Diminished ovarian reserve (DOR) is a challenging issue in in vitro fertilization (IVF) treatment, leading to low follicle counts, high cancellation rates, and decreased IVF success. Premature ovarian insufficiency and poor ovarian response are other challenging issues that account for a significant portion of IVF patients with DOR[1-3]. To date, numerous pharmacological add-on treatments have been applied to increase IVF success, including testosterone replacement therapy and growth hormone supplementation[4]. Recently, autologous platelet-rich plasma and exosome injections into ovaries have also been performed, resulting in an increase in antral follicle count, mature oocyte (M2) count, and pregnancy rates[5]. Additionally, in vitro maturation (IVM), which enhances IVF success since it allows for retrieval of mature oocytes from small antral follicles[6,7], is a treatment option that has become increasingly popular in recent years[6].

IVM is defined as an assisted reproductive technology (ART) involving in vitro maturation of immature oocytes collected from small antral follicles. There are numerous IVM regimens introduced in the literature, namely standard IVM, biphasic IVM, human chorionic gonadotrophin (hCG)-primed IVM, and rescue IVM[7]. In all these regimens, the key aim is to achieve IVM of immature oocytes without denudation of cumulus-oocyte complexes (COCs), mainly due to the bidirectional communication between oocyte and cumulus cells that supports oocyte growth and maturation[6,7]. However, this is the case in standard and biphasic IVM; cumulus cells are denuded in rescue IVM in order to distinguish mature and immature oocytes. Therefore, IVM success is significantly lower in rescue IVM. Accordingly, if mature and immature oocytes in small follicles can be differentiated before denudation in IVM, it may be possible to obtain a higher number of mature oocytes in conventional IVF patients.

In this study, we aimed to investigate the predictive value of morphological assessment of COCs prior to denudation in distinguishing mature and immature oocytes in conventional IVF cycles.

Materials and Methods

This is a single-center prospective observational study conducted at Acıbadem Maslak Hospital IVF department between February 1 and April 1, 2025. The study was approved by Acıbadem University Ethics Committee and was performed in accordance with the ethical standards described in the 1975 Declaration of Helsinki, as revised in 2000 (approval no: 2025-04/157, date: 06.03.2025). Informed consent was obtained from each patient prior to the study. On the 2nd or the 3rd day of the menstrual cycle, the uterus and bilateral adnexa were examined, and antral follicles were counted automatically by vaginal sonography. Estradiol and progesterone levels were also measured for each patient. The antagonist protocol was applied to all patients, and follicles were triggered by hCG, gonadotropin-releasing hormone agonist (GnRHa), or a combination of both. Oocyte retrieval was performed 36 hours after the trigger using transvaginal sonographic guidance, with a 17 G needle, under sedation. Approximately two hours later, COCs were denuded and immature oocytes were discarded, followed by the administration of intracytoplasmic sperm injection (ICSI) to mature oocytes.

The procedure was conducted by five embryologists with at least five years of experience. The study consisted of two stages:

First Stage

The first stage was undertaken by all five embryologists. After oocyte retrieval, COCs were evaluated under a microscope by one embryologist and they were distinguished as mature or immature based on their morphological appearance. Two hours later, COCs were denuded by another embryologist and the counts of mature and immature oocytes were recorded. The first stage was terminated when each embryologist had evaluated a minimum of 100 COCs.

Second Stage

The second stage was undertaken by three embryologists. The procedure in this stage was applied continuously for one more month to assess its effect on the success rate. Mature and immature oocytes were distinguished based on the following criteria:

1. COCs consisting of mature oocytes with an appearance of radiating corona cells surrounded by loose granulosa cells (GCs).
2. Cumulus cells showing a bright appearance under microscope.
3. COCs consisting of immature oocytes [germinal vesicles (GVs)] characterized by an unexpanded cumulus with multiple layers of compact GSs and a dark-brown appearance.

Statistical Analysis

All data were analyzed using SPSS (SPSS-IBM 2.3, Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to assess data normality. Categorical variables were compared using chi-square or Fisher's exact test. Continuous variables were expressed as mean ± a standard deviation (SD). Categorical variables were presented as frequencies (n) and percentages (%). Statistical significance was set at a p value of <0.05.

Results

A total of 80 patients were enrolled in the study, and 1039 COCs were examined, comprising 837 (80.6%) mature and 202 (19.4%) immature oocytes. In the first stage of the study, 69% of immature and 80% of mature oocytes were identified correctly by the embryologists.

Table 1 shows the success rates obtained in the identification of mature and immature oocytes in the first stage of the study. These rates varied between 78.86% to 90.21% and 65.69% to 79.72% for mature and immature oocytes, respectively, and there was no significant difference among the embryologists in terms of the success rates.

Table 2 presents a comparison of the two stages with regard to the success rates obtained by three embryologists. Although the identification rates of immature oocytes according to the COC's morphology increased in the second stage for all three embryologists, the only significant increase was observed for AA ($p<0.05$). In the identification of mature oocytes, however, the success rate for EK increased from 88.55% to 94.01%, while it decreased for the remaining two embryologists, though not significantly.

Table 3 demonstrates the correlation between the number of COCs retrieved and the success rates. Patients were divided into four groups according to the number of COCs retrieved: (i) 1-5, (ii) 6-10, (iii) 11-20, and (iv) >21. There was no significant difference among these groups with regard to success rates.

Table 1. Success rates of identifying mature and immature oocytes among embryologists

Embryologist ID	Immature (%) (median value)	Mature (%) (median value)
I	66.88	90.21
II	65.69	85.55
III	79.72	88.97
IV	73.06	86.27
V	68.18	78.86
Total	70.95	86.87

Discussion

The world's first IVF baby, Louise Brown, was born in 1978. Although there have been numerous advancements in the field of IVF since then, DOR remains a limiting factor for IVF procedures. To date, numerous treatment options have been used to improve the success rate of IVF in DOR patients; however, no serious progress has yet been made. IVM, particularly rescue IVM, can be a good option for improving pregnancy rates in patients with DOR. IVM is a well-known ART that was developed decades ago. However, it has not been adopted into routine practice and remains underutilized. There are numerous IVM regimens, namely standard IVM, biphasic IVM, hCG-primed IVM, and rescue IVM. In standard and biphasic IVM, follicles are stimulated using follicle-stimulating hormone analogues for an average of three days, and follicles are retrieved without hCG triggering. After retrieval, COCs are cultured in IVM medium for approximately 36 hours and then denuded. Subsequently, mature oocytes are subjected to ICSI[6,7]. During this period, cumulus cells are of paramount importance since COCs are a group consisting of oocytes and specialized GCs that support oocyte growth and maturation, and also protect oocytes from the microenvironment[8].

On the other hand, rescue IVM involves steps similar to those of conventional IVF, except for the IVM of GV or meiosis 1 (MI) oocytes. In rescue IVM, the follicles are stimulated by gonadotropins over an average period of 10-12 days and then triggered by GnRHa, hCG, or a combination of both. After retrieval, COCs are denuded and ICSI is performed on mature oocytes while immature oocytes are kept in IVM medium for approximately 24 hours[6,7]. At the end of this period, if GV or MI oocytes transform into metaphase II (MII) oocytes, ICSI is performed[6,7]. However, it is distinct from classical or biphasic IVM due to the denudation of COCs before IVM[6-8]. Therefore, the success rate of rescue IVM is not notably high because oocytes are subjected to IVM after denudation of COCs[6-8]. In a study by Lee et al.[9], rescue IVM was performed in patients with low functional ovarian reserve. Approximately three hours after oocyte retrieval, COCs were denuded and immature oocytes were matured in vitro. The authors concluded that rescue IVM in patients with low functional ovarian reserve improved the likelihood of pregnancy and delivery. However, recent studies

Table 2. Comparison of the predictive value of mature and immature oocytes among three embryologists between the first and the second stage of the study

Embryologist ID	Immature (%) (first stage of the study)	Immature (%) (second stage of the study)	p-value	Mature (%) (first stage of the study)	Mature (%) (second stage of the study)	p-value
I (MY)	66.88	85.0	p>0.05	90.21	81.6	p>0.05
II (EK)	65.69	81.82	p>0.05	85.55	94.01	p<0.05
III (AA)	73.06	97.14	p<0.05	86.27	78.57	p>0.05

suggest a decrease in the success of IVM treatment after COC denudation[10,11]. One of the main purposes of this study was to demonstrate the accuracy of morphological assessment of COCs in identifying mature and immature oocytes before denudation. The morphology of COCs provides valuable information about the maturity of oocytes. In the literature, there are a limited number of studies demonstrating the effectiveness of morphological assessment of COCs in the identification of mature and immature oocytes[12-14]. Our study showed a significant predictive value of morphological assessment of COCs, in identifying mature and immature oocytes. Specifically, mature oocytes were characterized by a bright appearance of COCs and loosely arranged GCs surrounding radiate cells, while immature oocytes exhibited a darker appearance with multilayered GCs. On the other hand, oocyte diameter may also be used to improve the accuracy of this identification. In a study with Pors et al.[12], the association between oocyte diameter and maturation rate was assessed. The authors classified the COCs according to the diameter of oocytes and reported that the diameter was positively associated with a higher incidence of MII. They also suggested that the diameter of MII oocytes was significantly larger than the diameter of GV oocytes[12]. A recent study by Batsry et al.[13] investigated the accuracy in predicting oocyte maturity before denudation and, in a similar way to our study, evaluated the success rate of experienced embryologists in differentiating MII and GV oocytes before denudation. They found that the embryologists correctly identified 90% of MII oocytes and 72.7% of GV oocytes. In a similar study, Hammitt et al.[14] assessed the ability of three embryologists to identify the maturity of oocytes before denudation and reported the rates of accuracy as 74%, 64%, and 47%. Unlike in previous studies, this study evaluated the accuracy rates of the embryologists over an extended period. The study noted that there was no significant change in the accuracy rates for the first embryologist, while the rate for the second embryologist increased over the first nine months before reaching a plateau. As for the third embryologist, the rate showed a continuous increase throughout the study and reached 72% at the end of 17 months[14]. Although we obtained similar findings, our study consisted of two stages of identification in a similar way to the study by Hammitt et al.[14]. Our findings also showed that embryologists who consistently made the distinction between MII and GV oocytes demonstrated greater success.

Table 3. The relationship between the number of cumulus-oocyte complexes and the prediction success

Oocyte category	Immature (%)	Mature (%)
Category I	83.33	95.0
Category II	91.29	81.07
Category III	77.58	86.55
Category IV	61.20	84.11
Total	79.00	85.70

Study Limitations

The first limitation of our study was its short duration. Particularly in the second phase, the study could have been planned for three months, or longer. The second limitation of our study was that there was a relatively small number of COCs evaluated by the embryologists.

Conclusion

Morphological assessment of COCs before denudation does not provide definitive results about oocyte maturity, but the success rate may be higher if the procedure is performed by the same embryologist. In conclusion, this method does not seem to have sufficient accuracy in identifying mature and immature oocytes before denudation and thus further studies are needed to explore a more accurate procedure.

Ethics

Ethics Committee Approval: The study was approved by Acıbadem University Ethics Committee and was performed in accordance with the ethical standards described in the 1975 Declaration of Helsinki, as revised in 2000 (approval no: 2025-04/157, date: 06.03.2025).

Informed Consent: Informed consent was obtained from each patient prior to the study.

Footnotes

Authorship Contributions

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

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