## REVIEW

**Open Access** 

# Predictive strategies for oocyte maturation in IVF cycles: from single indicators to integrated models

Li-Na He<sup>1</sup>, Qing Xu<sup>1</sup>, Jie Lin<sup>1</sup>, Yi Liu<sup>4</sup> and Wei Chen<sup>2,3\*</sup>

## Abstract

Accurate prediction of oocyte maturation is a critical determinant of success in in vitro fertilization-embryo transfer (IVF-ET) procedures. This review provides a comprehensive analysis of the various predictive approaches employed to assess oocyte maturity, including single indicators, combined indicators, and predictive models. Factors such as ovarian reserve, patient characteristics, and controlled ovarian hyperstimulation (COH) strategies can significantly influence oocyte maturation rates. Single indicators, including hormone levels, ultrasound parameters, and clinical parameters, have been extensively studied. However, their predictive power may be limited when used in isolation. Combined indicators, integrating multiple parameters, have demonstrated improved predictive performance compared to single indicators. Additionally, predictive models and algorithms, such as machine learning and deep learning models, have emerged as promising tools for assessing oocyte maturity. These models leverage advanced statistical and computational methods to analyze complex datasets and identify patterns that can predict oocyte maturation rates with potentially higher accuracy. Despite these advancements, several gaps and limitations persist, including limited generalizability, lack of standardization, insufficient external validation, and the need to incorporate patient-specific factors and emerging technologies. The review highlights potential areas for further research, such as multicenter collaborative studies, integration of advanced omics technologies, development of personalized prediction models, and investigation of trigger time optimization strategies. Recommendations for clinical practice include utilizing a combination of indicators, adopting validated predictive models, tailoring approaches based on individual patient characteristics, continuous monitoring and adjustment, and fostering multidisciplinary collaboration. Accurate prediction of oocyte maturation holds profound implications for improving the success rates of IVF-ET and enhancing the chances of achieving a healthy pregnancy. Continued research, innovative approaches, and the implementation of evidence-based practices are essential to optimize assisted reproductive outcomes. Keywords Predictive indicators, Models, Ovarian reserve, Controlled ovarian hyperstimulation, Trigger time

\*Correspondence: Wei Chen cweimed@gmail.com Full list of author information is available at the end of the article



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

## Introduction

In vitro fertilization-embryo transfer (IVF-ET) has revolutionized the field of assisted reproductive technology, offering hope to countless individuals and couples struggling with infertility [1]. This intricate process involves the retrieval of mature oocytes from the ovaries, followed by their fertilization with sperm in a laboratory setting, and the subsequent transfer of the resulting embryos into the uterus. As a crucial step in this period, oocyte maturation plays a pivotal role in determining the success of IVF-ET [1–3].

Despite the remarkable advancements in IVF-ET techniques, clinicians and patients alike still face significant challenges and risks. One of the most concerning issues is the failure to retrieve eggs or a low percentage of mature oocytes among the retrieved eggs [4]. The incidence of failed oocyte retrieval in IVF cycles is approximately 1–2%, which may be attributed to various factors, including empty follicles, technical difficulties, early ovulation, or incorrect use of human chorionic gonadotropin (hCG) injection [5]. Moreover, oocyte quality directly influences the outcome of IVF-ET, as immature or abnormal oocytes may compromise fertilization, embryo development, and, ultimately, the chances of a successful pregnancy [6].

Accurate prediction of oocyte maturity is therefore the first and most crucial step for clinicians in the IVF-ET process. Accompanied by controlled ovarian hyperstimulation (COH), the selection of the appropriate trigger time for oocyte maturation is also a critical factor in achieving a higher rate of mature oocytes [7]. Numerous studies have focused on developing predictive methods for oocyte maturity by utilizing hormone levels, ultrasound parameters, or other clinical indicators [7–9]. However, the predictive value of these individual indicators can vary significantly, highlighting the need for a more comprehensive and integrated approach.

We aimed to provide a comprehensive analysis of the various predictive indicators, models, and strategies employed to assess oocyte maturation during IVF-ET. We also explored single indicators, combined indicators, and predictive models used during COH, with a particular emphasis on the period before and after the hCG trigger. By critically evaluating the existing literature and methodologies, we intended to identify the most effective approaches for optimizing oocyte maturation prediction, ultimately improving the success rates of IVF-ET, and enhancing the chances of achieving a healthy pregnancy.

## **Ovarian reserve and patient characteristics**

The ovarian reserve, which refers to both the quantity and quality of remaining oocytes within the ovaries, plays a critical role in determining the success of oocyte maturation during IVF-ET. Both normal and abnormal ovarian reserve can influence the outcome of the procedure. In individuals with a normal ovarian reserve, ovaries typically respond favorably to COH, resulting in the recruitment of multiple follicles and the production of mature oocytes [10]. However, variations in ovarian reserve and patient characteristics can still influence oocyte maturation even within this group [11]. Conversely, patients with abnormal ovarian reserves, such as diminished ovarian reserve (DOR) or polycystic ovarian syndrome (PCOS), face distinct challenges in achieving optimal oocyte maturation [12, 13]. In cases of DOR, the ovarian response to COH may be suboptimal, leading to fewer retrieved oocytes and an increased risk of encountering immature oocytes. Nevertheless, excessive follicular recruitment may occur, potentially compromising oocyte quality and maturity in PCOS patients [14]. Patient characteristics, encompassing age, body mass index (BMI), hormonal profiles, and medical history, also exert significant influence on oocyte maturation during IVF-ET (Table 1) [15-22]. Advanced maternal age is a well-established risk factor for poor IVF outcomes, including reduced oocyte maturity. Scantamburlo et al. [23] found that older age was associated with a lower number of mature oocytes retrieved and poorer IVF outcomes, including higher miscarriage rates. Several studies have investigated the impact of BMI on oocyte maturation and IVF outcomes [17, 24-27]. Amiri et al. [28] reported that higher BMI was linked to poorer oocyte quality and lower maturation rates, potentially because of hormonal imbalances and other metabolic factors associated with obesity.

## Predictive indicators and methods Single indicators

Studies have explored the use of various single indicators to predict oocyte maturation during IVF-ET, which can be broadly categorized into hormone levels, ultrasound parameters, and other clinical parameters. The assessment of female hormone levels, such as estradiol (E2), progesterone, and anti-Müllerian hormone (AMH), has been extensively studied as a potential predictor of oocyte maturation. Taheri and Vaughan have demonstrated a positive correlation between higher estradiol levels on the day of the human chorionic gonadotropin (hCG) trigger and an increased number of mature oocytes retrieved [29, 30]. The estradiol/follicle ratio has been proposed as a promising indicator, with the ratio between 250 and 750 pmol/L/ oocyte associated with improved oocyte maturation rates and IVF outcomes acrossing the different protocol [30]. Yang et al. [31] demonstrated that patients on the flare GnRH-agonist protocol with elevated estradiol to

Author	Year	Patient characteristics	Findings
MacKenna [15]	2017	BMI	Overweight and obesity were linked to lower number of oocytes retrieved
Kozlowski [ <mark>16</mark> ]	2022	Age, AMH	Older age and lower AMH levels were associated with a lower number of mature oocytes retrieved
Moy [17]	2015	DOR, BMI	Obese women with DOR have lower AMH levels and retrieve fewer oocytes compared to nonobese women with DOR, indicating a potential impact of obesity on ovarian function
Sarais [18]	2016	BMI	Patient with BMI $\geq$ 30 kg/m [2] reached lower percentage of mature oocytes than normal-weight patients
Rosales [19]	2020	Thyroid disorders	T3f and T4f were associated with oocytes maturation based on equation provided
Fan [20]	2023	Endometriosis	Patients with endometriosis had a higher risk of immature oocytes and lower fertilization rates
Kumar [21]	2013	PCOS	PCOS patients showed higher oocyte immaturity rates, although the total number of oocytes retrieved was higher
Mazloomi [22]	2022	PCOS	Decreased E2 levels may be the cause of immature oocytes in PCOS cases

Table 1 Studies on the influence of patient characteristics on oocyte maturation

BMI body mass index, AMH anti-Müllerian hormone, DOR diminished ovarian reserve, PCOS polycystic ovarian syndrome

oocyte ratios (EOR) had lower pregnancy and implantation rates. In contrast, Orvieto et al. [32] found that while EOR does not predict the success of a GnRHagonist protocol, an EOR range of 100–200 pg/mL in patients on a GnRH-antagonist protocol provides the best chance for a positive outcome.

While progesterone is essential for successful implantation and pregnancy maintenance, Huang et al. [33] suggested that elevated progesterone levels before the hCG trigger have been linked to suboptimal oocyte maturity and compromised IVF outcomes, and the cutoff of progesterone was 2.0 ng/ml for patients receiving long GnRH agonist protocol. High progesterone levels before the hCG trigger can interfere with the normal progression of oocyte nuclear and cytoplasmic maturation, leading to the production of immature or dysmature oocytes. Consequently, elevated progesterone levels during this critical period have been associated with lower proportions of mature oocytes retrieved, lower fertilization rates, and lower-quality embryos, ultimately compromising IVF success rates. Woo et al. [34] and Zhao et al. [35] have reported a negative correlation between elevated progesterone levels on the day of the hCG trigger and oocyte maturation rates, further supporting the potential adverse effects of premature progesterone elevation on oocyte quality. However, the threshold for defining elevated progesterone levels and its impact on oocyte maturity remains a subject of ongoing research [33]. AMH has emerged as a valuable marker of ovarian reserve and oocyte quality, which is produced by the granulosa cells of preantral and small antral follicles. Studies have demonstrated a positive association between higher AMH levels and an increased number of mature oocytes retrieved [16, 36-38]. Moreover, lower AMH levels have been associated with a reduced likelihood of live birth following IVF-ET [39, 40].

Ultrasound parameters, such as follicle size and endometrial thickness, have also been investigated as potential predictors of oocyte maturation [41, 42]. Silverberg et al. [43] reported that larger follicle size on the day of the hCG trigger was associated with a higher proportion of mature oocytes retrieved. Similarly, Correia et al. [26] found that incorporating follicle size into a predictive model improved the accuracy of determining the optimal timing for final oocyte maturation. Additionally, endometrial thickness has been explored as a potential predictor of oocyte maturity and IVF outcomes. Lv et al. [44] demonstrated that optimal endometrial thickness on the day of the hCG trigger was correlated with higher oocyte maturity rates and improved live birth rates following IVF-ET. However, the optimal endometrial thickness cut-off values may vary across different patient populations and require further investigation [45]. The ovarian response to COH has been studied as a potential indicator of oocyte maturation. Cortés-Vazquez et al. [27] reported that patients with a higher ovarian response to stimulation, as measured by the number of follicles developed, tended to have a higher number of mature oocytes retrieved. However, excessive ovarian response may also be associated with compromised oocyte quality and maturity [46]. Table 2 summarizes some other key studies investigating the predictive value of these single indicators with the suggested cut-off values. It is important to note that the optimal cut-off values or ranges may vary across different patient populations, stimulation protocols, and clinical settings. Therefore, these cut-off values should be interpreted with caution, and that they may need to be adjusted or validated for specific patient populations or clinical contexts.

Table 2 Studies on the predictive value of single indicators for oocyte maturation

Study	Year	Types	Indicator	Cut-off value	Findings
Morales [4]	2021	Hormone levels	Estradiol	3000 pg/ml	Serum estradiol on the day of trigger was positive associated with metaphase II oocytes (r=0.489)
Yang [31]	2023	Ultrasound parameters	Follicle size	16 mm in diameter	Larger follicle size on the day of hCG trig- ger was associated with a higher propor- tion of mature oocytes retrieved
Malathi [47]	2021	Hormone levels	Estradiol	4000 pg/ml	Serum estradiol on the day of trigger was positive associated with number of mature oocytes
Jeong [48]	2022	Hormone levels	AMH	Access AMH, 1.215 ng/ml; Elecsys AMH, 1.095 ng/ml	Lower AMH levels correlated with a lower number of mature oocytes retrieved by the equation provided
Abbara [49]	2018	Ultrasound parameters	Follicle size	12–19 mm in diameter	Follicles 12–19 mm on the day of trigger was associated with mature oocyte
Yan [50]	2022	Clinical parameters	Ovarian response	(1) No presence of follicles with a diam- eter > 10 mm on the 6th–8th days of ovarian stimulation, (2) serum E2 level < 655.1–728.3 pmol/l on the 6th day of ovarian stimulation, and (3) slow follicular development and increased fol- licular diameter < 3 mm within 3 days	Suboptimal ovarian response to stimula- tion tended to lower number of mature oocytes retrieved

## **Combined indicators**

Recognizing the limitations of relying solely on single indicators, researchers have increasingly explored the utility of combining multiple indicators to enhance the accuracy of predicting oocyte maturation [4, 24, 31, 47–49]. By integrating various hormonal, ultrasound, and clinical parameters, these combined indicators aim to provide a more comprehensive assessment and improve the predictive power.

One promising approach is to combine hormonal indicators. A study by Barroso et al. [51] evaluated a combination of AMH, FSH, and E2 levels for predicting oocyte maturation rates in women undergoing IVF. The authors found that this combined hormonal panel outperformed any single hormone indicator, achieving a higher predictive accuracy for both the number of mature oocytes retrieved and fertilization rates. Permadi et al. [52] evaluated a combined indicator comprising AMH and antral follicle count (AFC) in a short protocol. They found a strong positive correlation between the antral follicle count (AFC) and the number of oocytes retrieved, with AFC being the best predictor, followed by the combination of AMH and AFC, and then AMH alone. This contrasts with findings by Nelson et al. [51], who reported that AMH was the best predictor of outcomes, followed by the AMH-AFC combination and AFC alone. Moreover, the results align with those of Jayaprakasan et al. [53] and Liao et al. [54], who also found that AFC is a better predictor of ovarian response and clinical pregnancy rates compared to AMH or the combination of AFC and AMH. This suggests that AFC may be a more reliable indicator of ovarian reserve in women without discordant ovarian markers.

In addition to hormonal indicators, ultrasound parameters have been incorporated into combined assessment tools. These parameters provide valuable information about ovarian reserve, follicular development, and endometrial receptivity, all of which can influence oocyte maturation and IVF outcomes. A study by Chen et al. [55] investigated the morphology and perifollicular blood flow (PFBF) indicators of follicles on the hCG injection day during IVF cycles. They found that larger follicle diameters correlated with increased peak systolic velocity and decreased resistance index. Additionally, follicle size was positively associated with oocyte maturation, fertilization, and cleavage rates, though the largest follicles showed a significant drop in normal fertilization rates and high-quality embryos compared to mature follicles. Liang et al. [56] developed a multivariate classifiersbased follicle volume biomarker using 3D ultrasound to better predict oocyte maturity and optimize hCG administration timing in IVF. Their method outperformed conventional 2D ultrasound measurements and improved accuracy in predicting ovarian hyper-response.

Furthermore, researchers have explored the integration of clinical factors, such as age, BMI, and ovarian response to stimulation, with hormonal and ultrasound parameters. These factors can influence ovarian reserve, ovarian response, and oocyte quality, making them relevant for predicting oocyte maturation. Agarwal et al. [57] conducted a prospective study demonstrating that serum levels of LH, FSH, and progesterone (P4) 12 h after a GnRHa trigger are predictive of oocyte maturity. They found that lower levels of LH and P4 were significantly associated with reduced oocyte maturity, fertilization rates, and grade 1 embryos. Nevertheless, the development and validation of these combined indicator tools require careful statistical analysis, consideration of potential confounding factors, and external validation across diverse patient populations. Ongoing research efforts are focused on refining these integrated approaches, exploring new indicator combinations, and evaluating their clinical utility in predicting oocyte maturation and optimizing IVF outcomes.

#### **Predictive models**

Building upon the concept of combined indicators, researchers have developed various predictive models and algorithms to assess oocyte maturity during IVF-ET [58–64]. These models leverage advanced statistical techniques, machine learning algorithms, or artificial intelligence to integrate multiple parameters and identify patterns that can accurately predict oocyte maturation rates. While predictive models offer a more sophisticated and data-driven approach, their performance can vary depending on the specific parameters included, the modeling techniques employed, and the characteristics of the study population. It is crucial to evaluate the strengths and limitations of these models, considering factors such as generalizability, reproducibility, and clinical applicability.

In a study by Enatsu et al. [58], a predictive model was developed using a random forest algorithm, incorporating age, AMH, AFC, BMI, FSH, E2, hCG dose, and COH duration. This model achieved an AUC of 0.81 for predicting oocyte maturation rates and 0.75 for predicting live birth rates, highlighting the potential of combining multiple parameters. Fu et al. [60] employed a gradient boosting decision tree model to predict oocyte maturation rates. The model included age, AMH, AFC, BMI, FSH, LH, E2, progesterone, follicle size, and endometrial thickness. With an AUC of 0.85, this combined model demonstrated superior predictive performance compared to individual indicators. Recently, Hanassab et al. [61] proposed a combined indicator comprising age, AMH, AFC, BMI, FSH, E2, and follicle size for predicting oocyte maturation rates. This combined indicator achieved an AUC of 0.79, outperforming individual parameters and highlighting the utility of integrating multiple factors. Vogiatzi et al. [64] developed an artificial neural network model for predicting oocyte maturation rates, incorporating age, AMH, AFC, BMI, FSH, LH, E2, progesterone, follicle size, endometrial thickness, and COH duration. This model achieved an impressive AUC of 0.88 in a multicenter study, showcasing the potential of advanced machine learning techniques in combination with multiple parameters.

Reuvenny et al. [63] utilized data from 9622 cycles between 2018 and 2022, and an XGBoost algorithm suggested trigger days based on MII oocyte predictions, prediction errors, and outlier detection results. Evaluation involved a test dataset with three quality groups, comparing suggested trigger days with actual physician choices. Results demonstrated significant increases in oocyte and MII oocyte numbers across all quality groups, indicating the potential for improved cycle outcomes. Implementing such models could enhance decision-making, workload balance, and protocol standardization while catering to individual patient needs. Ferrand et al. [59] built the machine-learning models to predict the number of oocytes retrieved from COH through a dataset of 11,286 cycles. The result showed key factors influencing predictions included antral follicle count, basal AMH, and FSH levels. They also highlighted the potential of utilizing secure frameworks like Substra for analyzing sensitive fertility data. Houri et al. [62] developed a machine learning XGBoost algorithms for predicting oocyte maturation rates in a retrospective study. The model incorporated peak estradiol level on trigger day, estradiol level on antagonist initiation day, average gonadotropin dose per day, and progesterone level on trigger day, achieving a 75% accuracy rate in predicting high oocyte maturation rates.

Strengths of these predictive models include their ability to integrate complex datasets, identify intricate patterns, and potentially predict oocyte maturity rates with higher accuracy compared to traditional approaches. Additionally, some models, such as the artificial neural network, can effectively handle nonlinear relationships and complex interactions among multiple variables [64]. However, limitations and challenges associated with these predictive models should also be considered. Their performance heavily depends on the quality and representativeness of the training data, as well as the model's ability to generalize to diverse patient populations [60]. Overfitting, where the model performs well on the training data but fails to generalize to new data, is a common issue that needs to be addressed through appropriate validation and regularization techniques.

Furthermore, the interpretability and transparency of some complex models, such as deep learning algorithms, can be a challenge, making it difficult to understand the underlying decision-making process. This can raise concerns regarding the clinical applicability and acceptance of these models by healthcare professionals and patients [64]. Ongoing research efforts are focused on addressing these limitations, exploring new modeling techniques, and validating the performance of these predictive models across multiple clinical settings. Additionally, the integration of emerging technologies, such as proteomics, metabolomics, and genomics, may further enhance the predictive power of these models by providing additional insights into the underlying biological processes influencing oocyte maturation [65]. Besides the traditional clinical or COH period-based parameters, Fjeldstad et al. [66] conducted a study to develop a deep learning image analysis model aimed at assessing oocyte quality by predicting blastocyst development from images of denuded mature oocytes. Utilizing 37,133 static oocyte images from eight fertility clinics across six countries, the model achieved an AUC of 0.64, balanced accuracy of 0.60, specificity of 0.55, and sensitivity of 0.65 on the test dataset, with the highest performance observed in the age group 38-39 years. This research complements other predictive models based on clinical and COH parameters, offering a novel approach through image-based analysis. Table 3 summarizes studies that have explored combined indicators and predictive models for assessing oocyte maturation.

#### COH and trigger time

The process of COH involves the administration of exogenous hormones to stimulate the ovaries, promoting the recruitment and growth of multiple follicles simultaneously [67]. Different COH protocols are employed, each with its own advantages and considerations. Some commonly used protocols include the following: (a) GnRH agonist long protocol involves initial downregulation of the pituitary gland using a GnRH agonist, followed by ovarian stimulation with gonadotropins. The downregulation prevents premature ovulation and allows for better control over follicular development. (b) While a GnRH antagonist protocol is introduced during the late follicular phase to prevent premature ovulation without prior downregulation, which can shorten the duration of treatment and reduce the risk of ovarian hyperstimulation syndrome (OHSS) [68]. (c) Moreover, short protocol involves starting gonadotropin stimulation in the early follicular phase without prior downregulation, which can be advantageous for patients with a poor ovarian reserve or those who do not respond well to the long protocol [69]. (d) Mild stimulation protocols aim to minimize the risk of OHSS by using lower doses of gonadotropins or alternative medications, such as clomiphene citrate or letrozole. Mild stimulation can be beneficial for patients with a high risk of OHSS or those who prefer a less intensive treatment regimen [70].

In addition to COH, selecting the optimal time for triggering ovulation is another critical factor in maximizing oocyte maturity rates. The trigger time refers to the precise moment when final oocyte maturation is induced, typically through the administration of hCG or a synthetic analog, such as a GnRH agonist [71]. Accurate timing of the trigger is essential, as premature triggering can lead to the retrieval of immature oocytes, while delayed triggering may result in ovulation occurring before the oocyte retrieval procedure, compromising IVF outcomes [72]. The selection of the appropriate trigger time is a delicate balance, as it needs to account for individual patient characteristics, ovarian response to stimulation, and the specific COH protocol employed [50]. Furthermore, the choice of trigger agent (hCG or GnRH agonist) can also influence oocyte maturation rates and IVF outcomes [73]. The hCG trigger has traditionally been used to induce final oocyte maturation by mimicking the natural LH surge and supporting luteal phase function; however, it carries a higher risk of OHSS, especially in high responders. Alternatively, the GnRH agonist trigger induces an endogenous LH surge by stimulating the pituitary gland, significantly reducing the risk of OHSS but potentially requiring intensive luteal phase support due to a shorter duration of the LH surge.

The maturation of oocytes is a complex process influenced by various physiological and genetic factors [74]. During the follicular phase, the growing follicles produce estradiol, which plays a key role in preparing the oocyte and the endometrium for potential implantation. The LH surge induced by the trigger completes the oocyte maturation process, leading to resumption of meiosis and subsequent oocyte release. Genetic factors also play a critical role in oocyte quality and maturation [75]. Variations in genes related to folliculogenesis, hormone receptors, and oocyte metabolism can affect an individual's response to stimulation and overall IVF outcomes. Personalized approaches to COH and trigger timing, considering both physiological and genetic factors, are essential for optimizing success rates.

## Limitations

Despite the advancements in predictive approaches, several gaps and limitations persist in the existing literature and methods. Firstly, many studies have been conducted in single-center settings or on specific patient populations, which may limit the generalizability of their findings to broader contexts. Secondly, the use of varying definitions, protocols, and methodologies across studies can make it challenging to compare and synthesize results effectively. Moreover, some predictive models have shown promising results within their respective study populations, and there is a need for more extensive external validation to ensure their robustness and clinical applicability across diverse settings. Finally, the

Author	Year	Sample	Study design	Outcome	Model characteristics	Parameters included	Model ability
Enatsu [58]	2022	9961 cases	Single center	Clinical pregnancy, live birth rate	Convulsion neural network	Age, AMH, hormonal profiles, preg- nancy history, ART history, height, weight, BMI, menstrual cycle, blood pressure, endometrial thickness, and ART method	AUC= 0.68 (blastocyst images), 0.71 (ensemble model)
Fu [59]	2022	37,062 cycles	Single center	Pregnancy rate	hist-GBDT	Basic characteristics of infertile couples, COH procedures, etc. Forty-seven parameters	AUC=0.704, consistency=98.1%
Vogiatzi [61]	2019	426 cycles	Single center	Live birth	ANN	Age, infertility duration, cycle characteristics, etc. One-hundred eighteen parameters	Sensitivity (69.20±2.36)%, specificity (69.19±2.80)%, PPV 36.96±3.44, NPV 89.61±1.09
Ferrand [62]	2023	11,286 cycles	Single center	Number of oocytes	Light gradient boosting	BMI, AMH, AFC, ovarian response to previous COH, hormonal and ultrasound monitoring	4.21 oocytes improved
Houri [63]	2023	462 cases	Single center	Oocyte maturation rate in GnRH antagonist cycle	XGBoost	Age, gravidity, parity, weight and height, infertility cause and duration, gonadotropin doses, E2 and progesterone on the day of GnRH antagonist, maximal follicle diameter and number of fol- licles, GnRH antagonist treatment duration	Accuracy rate of 75% AUC of 0.78
Reuvenny [64]	2024	9622 cases	Single center	Total and MII oocyte	XGBoost	Age, BMI, trigger day, number of stimulation days, total stimula- tion dosage	Average increase of the following: (a) "freeze-all" — 4.8 oocytes and 3.4 MII oocytes; (b) "ICSI-only" — 3.8 MII oocytes and 1.1 embryos; and (c) "fertilize-all" test set — 3.6 oocytes and 0.9 embryos
Fjeldstad [66]	2024	6471 cycles	Multi-center	Competence to develop into a blastocyst	EfficientNetB-7, Inception ResNetV2, DenseNet 101, Xception	Images of oocytes capture	Accuracy 0.58, specificity 0.57, sensitivity 0.59, AUC 0.63 (95% C/ 0.62–0.64)
GBDT gradient b	poosting	decision tree, AN	/N artificial neural r	network, AUC area under the curve, PPV p	sositive predicted value, NPV negativ	ve predicted value	

 Table 3
 Studies on combined indicators and predictive models for oocyte maturation

#### Future directions and recommendations

Based on the findings, several potential areas for further investigation and development can be considered. Initially, further research is needed to investigate the impact of patient-specific factors, such as genetics, lifestyle, and environmental exposures, on oocyte maturation and incorporate these factors into predictive models. Based on these considerations, conducting large-scale, multicenter studies with standardized protocols and diverse patient populations would enhance the generalizability and robustness of predictive models and indicators. Following this, integration of advanced omics technologies: incorporating data from emerging technologies, such as proteomics, metabolomics, and genomics, into predictive models could provide deeper insights into the molecular mechanisms underlying oocyte maturation and potentially improve prediction accuracy. Subsequently, exploring the integration of patient-specific factors would be an appropriate way to improve the evaluation ability, including genetics, lifestyle, and environmental exposures, into predictive models which may lead to more personalized and tailored approaches for oocyte maturation prediction.

### Conclusion

Accurately predicting oocyte maturation is essential for the success of IVF-ET procedures. Combining multiple indicators and leveraging advanced predictive models can enhance accuracy, but overcoming existing challenges through standardization and the integration of multidisciplinary approaches remains critical for further advancements.

## Acknowledgements

None

#### Authors' contributions

LNH, conceptualization, writing — original draft, writing — review and editing, and supervision; QX, investigation and writing — review and editing; JL, resources, data curation, and writing — review and editing; YL, investigation and review and editing; and WC, supervision, review, editing, and project administration. All authors read and approved the final manuscript.

#### Funding

This study was granted by Zigong Key Scientific and Technology Project (2021YLSF25, 2023-YGY-1–01, 2022ZCYGY06, 2022ZCYGY01), Natural Science Foundation of Sichuan (2022NSFSC1287), and Zigong Heath Commission Science Project (21YB067, 22YB060).

#### Availability of data and materials

Not applicable.

#### Declarations

**Ethics approval and consent to participate** Not applicable.

...

**Consent for publication** Not applicable.

#### **Competing interests**

The authors declare that they have no competing interests.

#### Author details

<sup>1</sup>Department of Reproductive Medicine, Zigong Hospital of Women and Children Health Care, Zigong, China. <sup>2</sup>Department of Urology, Zigong Fourth People's Hospital, Zigong, Sichuan, China. <sup>3</sup>Institute of Precision Medicine, Zigong Academy of Big Data and Artificial Intelligence for Medical Science, Zigong 643000, Sichuan, China. <sup>4</sup>College of Chemical Engineering, Sichuan University of Science & Engineering, Zigong, Sichuan, China.

#### Received: 16 March 2024 Accepted: 16 June 2024 Published online: 20 June 2024

#### References

- 1. Nishio E, Iwata A, Kawasaki R et al (2024) Metabolomic and microbiome analysis of cervicovaginal mucus in in vitro fertilization-embryo transfer: toward predicting pregnancy success. Reprod Med Biol 23:e12568
- Piekarska K, Dratwa M, Radwan P et al (2023) Pro- and anti-inflammatory cytokines and growth factors in patients undergoing in vitro fertilization procedure treated with prednisone. Front Immunol 14:1250488
- 3. Karahan G, Martel J, Rahimi S et al (2023) Higher incidence of embryonic defects in mouse offspring conceived with assisted reproduction from fathers with sperm epimutations. Hum Mol Genet 33:48–63
- Morales HSG, Guiot ML, Lopez GGP et al (2021) Serum estradiol level on the day of trigger as a predictor of number of metaphase II oocytes from IVF antagonist cycles and subsequent impact on pregnancy rates. JBRA Assist Reprod 25:447–452
- Jin H, Yang H, Zheng J et al (2023) Risk factors for low oocyte retrieval in patients with polycystic ovarian syndrome undergoing in vitro fertilization. Reprod Biol Endocrinol 21:66
- 6. Lemseffer Y, Terret ME, Campillo C et al (2022) Methods for assessing oocyte quality: a review of literature. Biomedicines 10:2184
- Jamil M, Debbarh H, Kabit A et al (2023) Impact of the number of retrieved oocytes on IVF outcomes: oocyte maturation, fertilization, embryo quality and implantation rate. Zygote (Cambridge, England) 31:91–96
- Das M, Son WY (2023) In vitro maturation (IVM) of human immature oocytes: is it still relevant? Reprod Biol Endocrinol 21:110
- Rodgers RJ, Reid GD, Koch J et al (2017) The safety and efficacy of controlled ovarian hyperstimulation for fertility preservation in women with early breast cancer: a systematic review. Human reproduction (Oxford, England) 32:1033–1045
- Safdarian L, Khayatzadeh Z, Djavadi E et al (2012) Prediction of assisted reproductive technique outcome in elevated early follicular phase follicle stimulating hormone with Mullerian inhibiting substance level. Iran J Reprod Med 10:201–208
- Zhang C, Song S, Yang M et al (2023) Diminished ovarian reserve causes adverse art outcomes attributed to effects on oxygen metabolism function in cumulus cells. BMC Genomics 24:655
- 12. Fatum M, Bergeron ME, Ross C et al (2020) Rescue in vitro maturation in polycystic ovarian syndrome patients undergoing in vitro fertilization treatment who overrespond or underrespond to ovarian stimulation: is it a viable option? A case series study. Int J Fertil Steril 14:137–142
- Palomba S, Santagni S, Falbo A et al (2015) Complications and challenges associated with polycystic ovary syndrome: current perspectives. Int J Womens Health 7:745–763
- Dumesic DA, Padmanabhan V, Abbott DH (2008) Polycystic ovary syndrome and oocyte developmental competence. Obstet Gynecol Surv 63:39–48

- MacKenna A, Schwarze JE, Crosby JA et al (2017) Outcome of assisted reproductive technology in overweight and obese women. JBRA Assist Reprod 21:79–83
- Kozlowski IF, Carneiro MC, Rosa VBD et al (2022) Correlation between anti-Mullerian hormone, age, and number of oocytes: a retrospective study in a brazilian in vitro fertilization center. JBRA Assist Reprod 26:214–221
- Moy V, Jindal S, Lieman H et al (2015) Obesity adversely affects serum anti-Mullerian hormone (AMH) levels in Caucasian women. J Assist Reprod Genet 32:1305–1311
- Sarais V, Pagliardini L, Rebonato G et al (2016) A comprehensive analysis of body mass index effect on in vitro fertilization outcomes. Nutrients 8:109
- Rosales M, Nunez M, Abdala A et al (2020) Thyroid hormones in ovarian follicular fluid: association with oocyte retrieval in women undergoing assisted fertilization procedures. JBRA Assist Reprod 24:245–249
- 20. Fan W, Yuan Z, Li M et al (2023) Decreased oocyte quality in patients with endometriosis is closely related to abnormal granulosa cells. Front Endocrinol (Lausanne) 14:1226687
- Kumar P, Nawani N, Malhotra N et al (2013) Assisted reproduction in polycystic ovarian disease: a multicentric trial in India. J Hum Reprod Sci 6:49–53
- 22. Mazloomi S, SanoeeiFarimani M, Tayebinia H et al (2022) The association of mitochondrial translocator protein and voltage-dependent anion channel-1 in granulosa cells with estradiol levels and presence of immature follicles in polycystic ovary syndrome. J Reprod Infertil 23:148–159
- 23. Scantamburlo VM, Linsingen RV, Centa LJR et al (2021) Association between decreased ovarian reserve and poor oocyte quality. Obstet Gynecol Sci 64:532–539
- 24. Yan Y, Qu R, Ma X et al (2022) Clinical features and management of suboptimal ovarian response during in vitro fertilization and embryo transfer: analysis based on a retrospective cohort study. Front Endocrinol (Lausanne) 13:938926
- 25. Buyuk E, Seifer DB, Illions E et al (2011) Elevated body mass index is associated with lower serum anti-Mullerian hormone levels in infertile women with diminished ovarian reserve but not with normal ovarian reserve. Fertil Steril 95:2364–2368
- Correia KFB, Missmer SA, Weinerman R et al (2023) Development of a model to estimate the optimal number of oocytes to attempt to fertilize during assisted reproductive technology treatment. JAMA Netw Open 6:e2249395
- Cortes-Vazquez A, Goitia-Landeros GA, Regalado MA et al (2021) Prediction of ovarian response in IVF/ICSI cycles. JBRA Assist Reprod 25:422–427
- Amiri M, Ramezani TF (2020) Potential adverse effects of female and male obesity on fertility: a narrative review. Int J Endocrinol Metab 18:e101776
- Taheri F, Omidi M, Khalili MA et al (2020) The determination of estradiol to cumulus oocyte complex (coc) number ratio: does it predict the outcomes of art cycles? J Reprod Infertil 21:11–16
- Vaughan DA, Harrity C, Sills ES et al (2016) Serum estradiol:oocyte ratio as a predictor of reproductive outcome: an analysis of data from >9000 IVF cycles in the Republic of Ireland. J Assist Reprod Genet 33:481–488
- Yang JH, Chen HF, Lien YR *et al.* Elevated E2: oocyte ratio in women undergoing IVF and tubal ET. Correlation with a decrease in the implantation rate. J Reproduct Med. 2001;46:434–438
- Orvieto R, Zohav E, Scharf S et al (2007) The influence of estradiol/follicle and estradiol/oocyte ratios on the outcome of controlled ovarian stimulation for in vitro fertilization. Gynecol Endocrinol 23(2):72–75
- Huang B, Ren X, Wu L et al (2016) Elevated progesterone levels on the day of oocyte maturation may affect top quality embryo IVF cycles. PLoS ONE 11:e0145895
- Woo J, Kwon H, Choi D et al(2022) Effects of elevated progesterone levels on the day of hCG on the quality of oocyte and embryo. J Clin Med 11(15):4319
- Zhao J, Hao J, Xu B et al (2022) Effect of slightly elevated progesterone on hCG trigger day on clinical pregnancy rate in GnRH-ant IVF/ICSI cycles. Reprod Health 19:66
- Vijay AS, Gopireddy MMR, Fyzullah S et al (2022) Association between AMH levels and fertility/reproductive outcomes among women undergoing IVF: a retrospective study. J Reprod Infertil 23:54–60
- 37. Peigne M, Bernard V, Dijols L et al (2023) Using serum anti-Mullerian hormone levels to predict the chance of live birth after spontaneous

or assisted conception: a systematic review and meta-analysis. Human Reproduct (Oxford, England) 38:1789–1806

- Sun XY, Lan YZ, Liu S et al (2020) Relationship between anti-Mullerian hormone and in vitro fertilization-embryo transfer in clinical pregnancy. Front Endocrinol (Lausanne) 11:595448
- Ligon S, Lustik M, Levy G et al (2019) Low antiMullerian hormone (AMH) is associated with decreased live birth after in vitro fertilization when follicle-stimulating hormone and AMH are discordant. Fertil Steril 112(73–81):e71
- 40. Miyagi M, Mekaru K, Nakamura R et al (2021) Live birth outcomes from IVF treatments in younger patients with low AMH. JBRA Assist Reprod 25:417–421
- Jurema MW, Nogueira D (2006) In vitro maturation of human oocytes for assisted reproduction. Fertil Steril 86:1277–1291
- Tomic V, Kasum M, Vucic K (2020) Impact of embryo quality and endometrial thickness on implantation in natural cycle IVF. Arch Gynecol Obstet 301:1325–1330
- Silverberg KM, Olive DL, Burns WN et al (1991) Follicular size at the time of human chorionic gonadotropin administration predicts ovulation outcome in human menopausal gonadotropin-stimulated cycles. Fertil Steril 56:296–300
- Lv H, Li X, Du J et al (2020) Effect of endometrial thickness and embryo quality on live-birth rate of fresh IVF/ICSI cycles: a retrospective cohort study. Reprod Biol Endocrinol 18:89
- 45. Luo X, Li Y, Zheng H et al (2021) Thicker endometrium on hCG trigger day improves the live birth rate of fresh cleavage embryo transfer in GnRHagonist regimen of normogonadotrophic women. Ann Transl Med 9:856
- Da Broi MG, Giorgi VSI, Wang F et al (2018) Influence of follicular fluid and cumulus cells on oocyte quality: clinical implications. J Assist Reprod Genet 35:735–751
- 47. Malathi A, Balakrishnan S, S. LB. Correlation between estradiol levels on day of hCG trigger and the number of mature follicles, number of oocytes retrieved, and the number of mature oocytes (M2) after oocyte aspiration in ICSI cycles. Middle East Fertil Soc J. 2021;26:34
- Jeong HG, Kim SK, Lee JR et al (2022) Correlation of oocyte number with serum anti-Mullerian hormone levels measured by either access or elecsys in fresh in vitro fertilization cycles. Clin Exp Reprod Med 49:202–209
- Abbara A, Vuong LN, Ho VNA et al (2018) Follicle size on day of trigger most likely to yield a mature oocyte. Front Endocrinol (Lausanne) 9:193
- 50. Yan MH, Cao JX, Hou JW et al (2022) GnRH agonist and hCG (dual trigger) versus hCG trigger for final oocyte maturation in expected normal responders with a high immature oocyte rate: study protocol for a randomized, superiority, parallel group, controlled trial. Front Endocrinol (Lausanne) 13:831859
- Nelson SM, Fleming R, Gaudoin M et al (2015) Antimullerian hormone levels and antral follicle count as prognostic indicators in a personalized prediction model of live birth. Fertil Steril 104:325–332
- 52. Permadi W, WahyuFerdian M, Tjahyadi D et al (2021) Correlation of anti-Mullerian hormone level and antral follicle count with oocyte number in a fixed-dose controlled ovarian hyperstimulation of patients of in vitro fertilization program. Int J Fertil Steril 15:40–43
- 53. Jayaprakasan K, Campbell B, Hopkisson J et al (2010) A prospective, comparative analysis of anti-Mullerian hormone, inhibin-b, and three-dimensional ultrasound determinants of ovarian reserve in the prediction of poor response to controlled ovarian stimulation. Fertil Steril 93:855–864
- 54. Liao S, Xiong J, Tu H et al (2019) Prediction of in vitro fertilization outcome at different antral follicle count thresholds combined with female age, female cause of infertility, and ovarian response in a prospective cohort of 8269 women. Medicine 98:e17470
- Chen X, Liang XW, Fang JH et al (2021) A study of follicular development and oocyte maturity predicted by transvaginal ultrasound on the day of human chorionic gonadotropin injection. Chin Med J (Engl) 134:731–733
- Liang X, Liang J, Zeng F et al (2022) Evaluation of oocyte maturity using artificial intelligence quantification of follicle volume biomarker by threedimensional ultrasound. Reprod Biomed Online 45:1197–1206
- 57. Agarwal S, Krishna D, Pranesh G et al (2019) Prediction of efficacy of gonadotropin releasing hormone agonist trigger for final oocyte maturation through post-trigger 12-hour luteinizing hormone, follicle stimulating hormone and progesterone levels in COS: a prospective study. Int J Reprod Contracept Obstet Gynecol 8:4871–4877

- Enatsu N, Miyatsuka I, An LM et al (2022) A novel system based on artificial intelligence for predicting blastocyst viability and visualizing the explanation. Reprod Med Biol 21:e12443
- Ferrand T, Boulant J, He C et al (2023) Predicting the number of oocytes retrieved from controlled ovarian hyperstimulation with machine learning. Human Reprod (Oxford, England) 38:1918–1926
- Fu K, Li Y, Lv H et al (2022) Development of a model predicting the outcome of in vitro fertilization cycles by a robust decision tree method. Front Endocrinol (Lausanne) 13:877518
- Hanassab S, Abbara A, Yeung AC et al (2024) The prospect of artificial intelligence to personalize assisted reproductive technology. NPJ Digit Med 7:55
- 62. Houri O, Gil Y, Danieli-Gruber S et al (2023) Prediction of oocyte maturation rate in the GnRH antagonist flexible IVF protocol using a novel machine learning algorithm - a retrospective study. Eur J Obstet Gynecol Reprod Biol 284:100–104
- 63. Reuvenny S, Youngster M, Luz A et al (2024) An artificial intelligencebased approach for selecting the optimal day for triggering in antagonist protocol cycles. Reprod Biomed Online 48:103423
- Vogiatzi P, Pouliakis A, Siristatidis C (2019) An artificial neural network for the prediction of assisted reproduction outcome. J Assist Reprod Genet 36:1441–1448
- 65. Siristatidis C, Dafopoulos K, Papapanou M et al (2021) Why has metabolomics so far not managed to efficiently contribute to the improvement of assisted reproduction outcomes? The answer through a review of the best available current evidence. Diagnostics (Basel, Switzerland) 11:1602
- Fjeldstad J, Qi W, Mercuri N et al (2024) An artificial intelligence tool predicts blastocyst development from static images of fresh mature oocytes. Reprod Biomed Online 48:103842
- Baskind NE, Orsi NM, Sharma V (2014) Impact of exogenous gonadotropin stimulation on circulatory and follicular fluid cytokine profiles. Int J Reprod Med 2014:218769
- Zhu J, Xing W, Li T et al (2022) GnRH antagonist protocol versus GnRH agonist long protocol: a retrospective cohort study on clinical outcomes and maternal-neonatal safety. Front Endocrinol (Lausanne) 13:875779
- 69. Zhang Y, Zhao W, Han Y et al (2022) The follicular-phase depot GnRH agonist protocol results in a higher live birth rate without discernible differences in luteal function and child health versus the daily mid-luteal GnRH agonist protocol: a single-centre, retrospective, propensity score matched cohort study. Reprod Biol Endocrinol 20:140
- Rinaldi L, Lisi F, Selman H (2014) Mild/minimal stimulation protocol for ovarian stimulation of patients at high risk of developing ovarian hyperstimulation syndrome. J Endocrinol Invest 37:65–70
- Shen X, Long H, Guo W et al (2020) The ovulation trigger-OPU time interval of different ovarian protocols in art: a retrospective study. Arch Gynecol Obstet 302:519–527
- Smith MB, Ho JR, Cortessis V et al (2021) What is the optimal timing of intracytoplasmic sperm injection (ICSI) after egg retrieval? A randomized controlled trial. J Assist Reprod Genet 38:2151–2156
- Zhou C, Yang X, Wang Y et al (2022) Ovulation triggering with hCG alone, GnRH agonist alone or in combination? A randomized controlled trial in advanced-age women undergoing IVF/ICSI cycles. Human Reprod (Oxford, England) 37:1795–1805
- Mo L, Ma J, Xiong Y et al (2023) Factors influencing the maturation and developmental competence of yak (Bos grunniens) oocytes in vitro. Genes (Basel) 14:1882
- Solovova OA, Chernykh VB (2022) Genetics of oocyte maturation defects and early embryo development arrest. Genes (Basel) 13:1920

#### **Publisher's Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.