

Retrospective Analysis

Oocyte maturity rate is an age-independent predictor of blastocyst development and euploidy rates: a multicenter retrospective study

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Research Question

Can oocyte maturity rate predict blastocyst development and euploidy rates independently of patient age?

Design

A multicenter retrospective study including 1547 consecutive women undergoing first in-vitro fertilization cycle of oocyte retrieval-intracytoplasmic sperm injection with preimplantation genetic testing for aneuploidy (IVF/ICSI/PGT-A). Both centers used the same PGT lab for PGT-A testing. Oocyte maturity rate as a predictor for cycle outcomes of blastocyst development and euploidy rates was analyzed by Poisson regression model, after controlling for other known confounders.

Results

Oocyte maturity rate is positively correlated with blastocyst development rate and euploidy rate after controlling for patient age at cycle start, BMI, AMH levels, total FSH dosage, number of days of ovarian stimulation, and peak estradiol level ($p < 0.01$).

Conclusion

This study demonstrated that oocyte maturity rate can predict blastocyst development and euploidy rates independently of other confounding factors including patient age. This finding suggests that oocyte maturity rate may serve as an important biomarker for oocyte quality. This can be used by physicians to evaluate and improve the efficacy of ovarian stimulation regimens for IVF. This may further enhance artificial intelligence (AI) capabilities in optimizing ovarian stimulation protocols and outcomes of Assisted Reproductive Technologies (ART).

INTRODUCTION

The ultimate goal of ovarian stimulation for IVF is to produce an optimal number of mature oocytes without risking women with severe ovarian hyperstimulation complication. Thus, the number of oocytes retrieved has often been used as a key parameter to evaluate the efficacy of ovarian stimulation protocols and different regimens for triggering final

maturation of follicles/oocytes prior to retrieval.^{1,2} However, the number and, more importantly, the quality of oocytes retrieved have long been recognized as important factors that affect IVF treatment outcome.^{3,4}

It has been well documented that maternal age significantly affects ovarian reserve but also oocyte quality.⁵ While Anti-Müllerian hormone (AMH), a biomarker of ovarian reserve, can reliably predict oocyte yield, conflict-

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ing reports exit on its ability to predict oocyte quality probably because correlation between AMH levels and oocyte quality is age-dependent.⁶⁻⁹ Oocyte maturation is controlled by gonadotropins and can affect embryo development.¹⁰⁻¹⁴ Furthermore, aneuploidy rate of embryos can be attributed to meiotic errors during oocyte maturation and advanced maternal age.^{15,16} Recent studies suggest that cohort oocyte maturity are correlated with embryo development rate and IVF treatment outcome.¹⁷⁻¹⁹ These studies, nevertheless, did not clarify the role of maternal age role in their findings.

The aim of this study was to investigate whether or not the relationships between oocyte quality, measured by maturity rate, and blastocyst and euploidy rates, are age dependent.

MATERIALS AND METHODS

Fifteen hundred forty-seven women undergoing first ICSI/PGT-A cycle from February 2020 to August 2023 were included in this multicenter study. All PGT-A testing was performed at the same PGT laboratory (Progenesis, La Jolla, CA). Nine hundred thirteen women underwent ICSI/PGT-A treatment at the Institute for Human Reproduction (IHR) in Chicago, IL, and 634 at Advanced Fertility Care (AFC) in Scottsdale, Arizona. Inclusion criteria were women age between 25-45 years old at cycle start, a minimum AMH of 0.20 ng/mL, maximal day-3 FSH of 15.0 mIU/mL, and BMI between 20-50. Donor oocyte cycles were excluded from the study.

Similar standard operating procedures were followed by IHR and AFC regarding patient management, ovarian stimulation, oocyte retrieval, fertilization by ICSI, embryo culture, and embryo biopsy.²⁰ Briefly, ovarian stimulation with antagonist suppression was the predominant protocol used in both IVF centers with a gonadotropins daily dosage of 150-600 IU based on patients' age and ovarian reserve. Pre-ovulatory triggers with GnRH agonist or recombinant hCG were administered with the same criteria in both centers, i.e. when the leading three follicles reached an average diameter of ≥ 17 mm. Oocyte retrieval procedures were performed 36 hours after the trigger shot. In both centers' embryology laboratories, oocyte maturity was determined 4-5 hours after oocyte retrieval through the identification of the 1st polar body of the denuded oocytes, and the oocytes were fertilized by ICSI. Oocytes at the MI or germinal vesicle stage 5 hours after oocyte retrieval were considered as not mature and were not subjected to ICSI treatment. The embryos were cultured for 5-7 days and the blastocysts were graded using Gardner's criteria²¹ in both embryology laboratories. Only blastocysts that reached a grading of 3BB or better were considered usable blastocysts and were biopsied for PGT-A. Embryo biopsy for PGT-A was performed by experienced embryologists, and the embryos were cryopreserved by vitrification after biopsy.

Before pooling the data, key parameters were compared and found to be similar between the 2 clinic datasets: 72% and 74% for oocyte maturity rates, 74% and 79% for fertil-

ization rate, 54% and 51% for blastocyst rate, and 49% and 51% for euploidy rate ($P > 0.05$).

Pearson's correlation coefficient analysis was conducted for all the baseline characteristics to determine if there was any correlation between the co-variables. Understanding that relationship was useful since highly correlated variables should be excluded from the multivariable regression model. Since only a medium correlation (Correlation coefficient = 0.4375) was found between AMH and Estradiol value, all the co-variables were included in the multivariable regression analysis.

Poisson regression analysis was employed to investigate the possible association of oocyte maturity with blastocyst rate and euploidy rate. Poisson regression is a statistical method used to model count data or the rate at which events occur. It estimates the relationship between predictor variables and the expected count or rate of an outcome, assuming the outcome follows a Poisson distribution, which is typically applied when the outcome data are non-negative integers but are not continuous.²² Blastocyst rate and euploidy rate can not be negative or greater than 100 %.

The Poisson regression models were adjusted for several potential confounders that may influence oocyte maturity, blastocyst formation, and euploidy rate, including maternal age at cycle start, BMI, AMH levels, total FSH dosage, number of days of ovarian stimulation, and peak estradiol level.^{5-9,23-26} Controlling these variables minimizes the potential for confounding bias and ensures that the observed associations between oocyte maturity and the outcome variables are accurately estimated.

Furthermore, stratification analyses were conducted by age group to evaluate whether the observed associations between oocyte maturity and blastocyst/euploidy rates were independent of maternal age. The estimates from the model output captured the average effect from the primary predictor and different confounders on the outcomes, i.e., whether the variable effect would reduce or increase the rate of outcomes. In addition, the strength of the effect from each of the variables was evaluated through the statistical test significance, i.e., P value, at a 95% confidence interval.

This retrospective study was reviewed and approved by the Pinnacle Research Ethics Committee (Accession # REC230412E).

RESULTS

EFFECTS OF PATIENT AGE AND CYCLE CHARACTERISTICS ON OOCYTE MATURITY AND BLASTOCYST AND EUPLOIDY RATES

Patient demographics and cycle characteristics are presented in [Table 1](#).

[Table 2](#) presents the descriptive statistics for oocyte maturity rate, blastocyst rate, and euploidy rate by age group, fertility types (diagnosis or reasons for IVF/ICSI/PGT treatment), ovarian stimulation protocols, and ovulatory trigger type. ANOVA tests showed that there were no statistically

TABLE 1. Patient and cycle characteristics and outcomes

Parameters	MEAN (STD)	MEDIAN (RANGE)
Age at cycle start	35.56 (4.31)	36 (23 - 45)
BMI	26.18 (5.52)	24.90 (18.00 - 44.90)
AMH	3.25 (2.97)	2.45 (0.01 - 32.10)
Days of stimulation	10.38 (1.41)	10 (7 - 16)
Total FSH dosage	2153.32 (1247.98)	1875 (125 - 7200)
Peak estradiol (ng/ml)	2112.44 (1119.97)	1884 (404 - 5999)
Number of oocytes retrieved	15.6 (10.12)	13 (1 - 74)
Oocyte maturity rate	0.74 (0.19)	0.77 (0.00 - 1.00)
Fertilization Rate by ICSI	0.78 (0.21)	0.79 (0.00 - 1.00)
Blastocyst rate	0.54 (0.25)	0.50 (0.00 - 1.00)
Euploidy rate	0.49 (0.27)	0.50 (0.00 - 1.00)

• Range was defined as minimum through maximum.

significant differences in oocyte maturity rate among any group of variables as P values were above 0.05. Blastocyst rates were significantly different among age groups and fertility types, and euploidy rates were significantly different among all groups of variables. Missing/Unknown categories were not included in descriptive statistics.

OOCYTE MATURITY RATE WAS POSITIVELY CORRELATED WITH BOTH BLASTOCYST RATE AND EUPLOIDY RATE

[Table 3](#) depicts the full output of the multivariable analysis of the effect on blastocyst rate and euploidy rate by oocyte maturity rate through Poisson regression model. The results indicated that oocyte maturity rate positively predicted the increase of both blastocyst rate and euploidy rate (EST = 1.0652 [0.8232 – 1.2928]; EST = 1.0287 [0.7976 – 1.2597], respectively). When data from the two IVF centers were analyzed separately, the same trend was observed but statistical significance was not reached likely due to smaller sample sizes.

Patient age was inversely correlated with blastocyst rate and euploidy rate (EST = -0.0158 [-0.0216 – -0.0099]; EST = -0.0395 [-0.0477 – -0.0312], respectively). Furthermore, AMH and estradiol value showed a negative effect on the blastocyst rate with statistical significance.

OOCYTE MATURITY RATE WAS AN AGE-INDEPENDENT PREDICTOR OF BLASTOCYST DEVELOPMENT AND EUPLOIDY RATE

In [Table 4](#), the correlation of oocyte maturity with blastocyst rate and euploidy rate, after stratifying by age group, was analyzed using Poisson regression model to evaluate whether the correlations were independent of patient age. Based on the outputs, the correlations were significant for all the age groups except the above 42 age group. A pos-hoc power analysis was conducted on this age category (n = 67) and the results indicated that the sample size was not sufficient to derive a significant result (power = 0.43). Therefore, oocyte maturity rate was an age-independent predictor of blastocyst development and euploidy rate.

Supplementary Tables 1 through 3 presents pairwise comparisons of oocyte maturity rate, blastocyst rate, and euploidy rate by each group were conducted through TUKEY test / t-test in. Stratification models were accessed to check the predicted independence for other confounding variables (ovulatory trigger type, infertility types, and ovarian stimulation protocols) and are presented in supplementary Tables 4.

DISCUSSIONS AND CONCLUSION

The primary goal of an optimal ovarian stimulation regimen is to yield a cohort of mature oocytes competent for fertilization and blastocyst formation in vitro and for implantation after embryo transfer. Although oocyte quality has been recognized to be more important than quantity, there are no reliable biomarkers for evaluating oocyte quality other than the presence of the first polar body, which represents only the completion of nuclear maturation.

This study demonstrates that cohort oocyte maturity rate is positively correlated with blastocyst formation within multiple age groups. These findings may help to explain the correlation between lower oocyte maturation and poor embryo development and IVF outcome that has reported in previous studies.¹⁷⁻¹⁹ More clinically significant, our study demonstrates that, unlike AMH levels, oocyte maturity was positively correlated with blastocyst rate and euploidy rate independent of patient age.

It is well established that increased maternal age is highly correlated with increased incidence of aneuploidy in both naturally conceived embryos and embryos resulting from IVF.^{15,16} Some other factors, including patient ovarian reserve, ovarian stimulation protocols, and types of ovulatory triggers may also affect the blastocyst development and/or euploidy rate. In this study, we found that AMH levels, a widely used biomarker for ovarian reserve, were negatively correlated with blastocyst rate but not with euploidy rate. However, this relationship is age-dependent and becomes absent when controlled by age. Similarly, a negative, age-dependent correlation was observed between

TABLE 2. Descriptive Statistics of Oocyte Maturity Rate, Blastocyst Rate, and Euploidy Rate by Age Group, Infertility Types, Ovarian Stimulation Protocols, and Ovulatory Trigger Type

Parameter	N (%)	Oocyte maturity rate		Blastocyst rate		Euploidy rate	
		MEAN (STD)	P VALUE	MEAN (STD)	P VALUE	MEAN (STD)	P VALUE
Age Group							
<35	628 (40.6%)	0.75 (0.18)	0.3124	0.57 (0.23)	<.0001	0.59 (0.23)	<.0001
35-37	384 (24.8%)	0.75 (0.19)		0.59 (0.24)		0.55 (0.24)	
38-40	328 (21.2%)	0.73 (0.18)		0.51 (0.26)		0.38 (0.25)	
41-42	140 (9.1%)	0.72 (0.22)		0.43 (0.25)		0.21 (0.23)	
42+	67 (4.3%)	0.75 (0.24)		0.30 (0.29)		0.17 (0.26)	
Infertility Types							
Missing	76 (4.9%)	-	0.5267	-	0.0002	-	0.0013
Diminished Ovarian Reserve	100 (6.5%)	0.72 (0.21)		0.52 (0.31)		0.40 (0.32)	
Male/Tubal/Ovulatory disorders	1054 (68.1%)	0.75 (0.18)		0.53 (0.25)		0.51 (0.27)	
Recurrent Pregnancy Loss	168 (10.9%)	0.73 (0.20)		0.62 (0.24)		0.52 (0.28)	
Unexplained	149 (9.6%)	0.74 (0.20)		0.52 (0.24)		0.46 (0.25)	
Ovarian Stimulation Protocols							
Missing	244 (15.8%)	-	0.6300	-	0.1984	-	0.0026
Microdose GnRH Agonist Flare	191 (12.4%)	0.73 (0.20)		0.51 (0.29)		0.43 (0.32)	
Antagonist	1112 (71.9%)	0.74 (0.18)		0.53 (0.24)		0.50 (0.26)	
Ovulatory Trigger Type							
Missing	21 (1.4%)	-	0.1600	-	0.8017	-	<.0001
GnRH Agonist	940 (60.8%)	0.75 (0.17)		0.54 (0.22)		0.53 (0.24)	
HCG Only	523 (33.8%)	0.73 (0.22)		0.53 (0.30)		0.43 (0.31)	
HCG and GnRH Agonist	63 (4.1%)	0.74 (0.18)		0.55 (0.23)		0.46 (0.28)	

- Abbreviation: GnRH – Gonadotropin-releasing hormone; HCG – Human chorionic gonadotropin.
- Missing/Unknown categories were not included in descriptive statistics.
- ANOVA tests were conducted to check the statistical significance of difference of Oocyte maturity rate, blastocyst rate, and euploidy rate within each group.
- Bolded P value indicated statistical significance within 95% confidence interval, i.e., $P < 0.05$.
- Pairwise Comparison of Oocyte Maturity Rate, Blastocyst Rate, and Euploidy Rate by Age Group, Infertility Type, and Ovulatory Trigger Type were conducted through TUKEY test / t test

TABLE 3. Multivariable Analysis on Blastocyst Rate and Euploidy Rate by Oocyte maturity Rate through Poisson Regression Model

Parameter	Blastocyst rate (n = 1547)		Euploidy rate (n = 1547)	
	EST [95% CI]	P VALUE	EST [95% CI]	P VALUE
Oocyte maturity rate	1.0652 [0.8232 - 1.2928]	0.0008	1.0287 [0.7976 - 1.2597]	<.0001
Patient age at cycle start	-0.0158 [-0.0216 - -0.0099]	<.0001	-0.0395 [-0.0477 - -0.0312]	<.0001
BMI	-0.0041 [-0.0084 - 0.0002]	0.0586	0.0018 [-0.0042 - 0.0078]	0.5618
AMH	-0.0089 [-0.0176 - -0.0003]	0.0431	-0.0031 [-0.0152 - 0.009]	0.6129
Total FSH dosage	0.0191 [-0.0088 - 0.0471]	0.1799	-0.0221 [-0.0619 - 0.0177]	0.2771
Days of stimulation	-0.0122 [-0.0328 - 0.0084]	0.2446	0.0058 [-0.0228 - 0.0343]	0.6925
Peak estradiol	-0.0319 [-0.0542 - -0.0096]	0.0051	-0.0003 [-0.0313 - 0.0307]	0.9851

- Poisson regression models were conducted for both univariable and multivariable analyses.
- The Wald Chi-Square tests were conducted to check the statistical significance.
- Bolded P value indicated statistical significance within 95% confidence interval, i.e., $P < 0.05$.

peak estradiol level and blastocyst rate. The effect of peak estradiol levels on oocyte developmental potential is likely to be age-dependent as previous studies on oocyte donors have found that high peak estradiol levels had no detrimen-

tal effect on oocyte quality and subsequent embryo development^{27,28}

Euploidy rates were reduced in patients with diminished ovarian reserve as an infertility diagnosis and in patients in cycles using micro-dose GnRH-a flare protocol to stimulate

TABLE 4. Multivariable Analysis on Blastocyst Rate and Euploidy Rate by Oocyte maturity Rate through Poisson Regression Model, stratified by Age Group

Parameter	Blastocyst rate		Euploidy rate	
	EST [95% CI]	P VALUE	EST [95% CI]	P VALUE
Age Group				
< 35 (n = 628)	1.0902 [0.3156 - 1.8352]	0.0029	0.9715 [0.6686 - 1.2743]	<.0001
35 - 37 (n = 384)	1.1174 [0.4289 - 2.1941]	0.0001	0.8020 [0.3511 - 1.2530]	0.0005
38 - 40 (n = 328)	1.0557 [0.3455 - 1.7570]	0.0054	1.2065 [0.5518 - 1.8613]	0.0003
41 - 42 (n = 140)	1.2821 [0.9201 - 1.6559]	0.0062	1.4782 [0.0208 - 2.9356]	0.0468
42+ (n = 67)	1.8353 [-0.4961 - 2.1668]	0.2188	1.7858 [-2.1983 - 5.7699]	0.3797

- Poisson regression models were conducted for both univariable and multivariable analyses.
- The Wald Chi-Square tests were conducted to check the statistical significance.
- Multivariable analyses were conducted by adjusting of age, BMI, indicator of ovarian reserve, medication dosage, days of treatment, and estradiol value.
- Bolded P value indicated statistical significance within 95% confidence interval, i.e., $P < 0.05$.

ovarian follicular growth or hCG to trigger final follicular maturation. All these correlative relationships were age-dependent.

Our findings that oocyte maturity rate may serve as an indicator for oocyte quality independent of patient age are clinically important because by monitoring oocyte maturity rate it can help reproductive specialists to optimize personalized ovarian stimulation protocols and ultimately improve treatment outcome. As AI technology is increasingly utilized in ART,²⁹⁻³¹ data that can independently predict treatment outcome, such as oocyte maturity, are needed for enhancing AI capabilities to optimize patient management and ART outcomes. The limitations of this study are that it is a retrospective study and uses data collected from two different fertility centers. Retrospective studies are inherently limited because of the lack of randomization in patient selection. While both centers used similar protocols, it is possible that there were unintended differences in medication dosage, time of trigger prior to oocyte retrieval, embryology practices, and embryo biopsy technique. This study is further limited due to missing data. All these limitations could introduce bias to data analysis results and interpretation. Further prospective studies with larger cohort sizes and standardized data collection are warranted to confirm findings of this study.

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COMPETING INTEREST

none

SUBMISSION DECLARATION

- The work has not been published previously.
- It is not under consideration for publication elsewhere.
- All authors and the responsible authorities where the work was carried out tacitly or explicitly approve of its publication.
- If accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically, without the written consent of the copyright holder.

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SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLES

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