Low oocyte maturity ratio is associated with a reduced in vitro fertilization and intracytoplasmic sperm injection live birth rate

Emily Capper, B.A.,[a] Michelle Krohn, D.O.,[b] Karen Summers, M.P.H.,[a] Rachel Mejia, D.O.,[a] Amy Sparks, Ph.D.,[a] and Bradley J. Van Voorhis, M.D.[a]

[a] Department of Obstetrics and Gynecology, University of Iowa Carver College of Medicine, Iowa City, Iowa; and [b] Department of Obstetrics and Gynecology, Monument Health, Spearfish, South Dakota.

Objective: To determine whether a low oocyte maturity ratio in a cohort of oocytes from an in vitro fertilization cycle predicts outcomes and to examine clinical factors associated with oocyte maturity.
Design: A retrospective cohort study.
Setting: An academic medical center.
Intervention(s): Determination of oocyte maturity immediately after the retrieval and 6 hours later if intracytoplasmic sperm injection was performed.
Main Outcome Measure(s): The primary outcome was live birth rate after the first embryo transfer. Secondary outcomes included clinical pregnancy, miscarriage, and fertilization rates.
Result(s): After adjusting for age, preimplantation genetic testing, and number of embryos transferred, we found that a low oocyte maturity ratio was associated with a decreased live birth rate (adjusted odds ratio [AOR], 0.41; 95% confidence interval [CI], 0.22–0.77) and clinical pregnancy rate (AOR, 0.32; 95% CI, 0.17–0.61). We did not find a relationship between oocyte maturity and miscarriage rate (AOR, 0.25; 95% CI, 0.03–1.91) or fertilization rate (Welch test). The number of 2 pronuclei embryos per retrieved oocyte was found to be associated with the maturity ratio at retrieval. Patients with anovulation had slightly reduced oocyte maturity compared with other diagnostic groups.
Conclusion(s): Low oocyte maturity ratio is an important factor related to poor in vitro fertilization outcomes, including decreased pregnancy and live birth rates. (Fertil Steril® 2022;118:680-87. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Oocyte maturity, fertilization, implantation, ICSI, IVF

DIALOG: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/34062

Oocyte maturation is critical to the process of human in vitro fertilization (IVF). Nuclear maturation is commonly judged by the stage of meiosis that has been completed by the oocyte and a range of maturity, including germinal vesicle, metaphase I (MI), and metaphase II (MI) oocytes that are commonly found in the cohort of oocytes retrieved from a woman (1). Cytoplasmic maturation of the oocyte is also known to occur, but this is more difficult to assess in the clinical setting (2). In our clinic, nuclear oocyte maturity is judged at 2 time points, immediately after retrieval in all patients while the oocyte is enclosed in cumulus cells and in the subset of patients using intracytoplasmic sperm injection (ICSI) for insemination, approximately 6 hours later when the cumulus cells are stripped away from the oocyte allowing better visualization of the nuclear maturity. Because oocytes mature in vitro in the hours after retrieval (3), the percentage of mature oocytes may differ between these 2 time points.

Although oocyte maturity is commonly assessed, little is known about the clinical factors that affect the ratio of mature oocytes to total oocytes in a cohort of retrieved oocytes and whether this ratio is a predictor of clinically important outcomes from an IVF cycle (2, 4–6). Therefore, our primary objective was to determine whether oocyte maturity ratio is a predictor of live birth rate after the first embryo transfer. Other outcomes of interest were the fertilization, clinical pregnancy, and miscarriage

Received October 13, 2021; revised July 11, 2022; accepted July 12, 2022.
E.C. has nothing to disclose. M.K. has nothing to disclose. K.S. has nothing to disclose. R.M. has nothing to disclose. A.S. has nothing to disclose. B.J.V.V. has nothing to disclose.
Correspondence: Bradley J. Van Voorhis, M.D., 31330 PFP, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242 (E-mail: brad-van-voorhis@uiowa.edu).

Fertility and Sterility® Vol. 118, No. 4, October 2022 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2022.07.008

rates after IVF. Our secondary objective was to identify the clinical factors associated with the oocyte maturity ratio.

MATERIALS AND METHODS

Study Inclusion and Exclusion Criteria

All autologous oocyte IVF cycles with retrieval of at least 1 oocyte between January 2016 and July 2019 at our academic IVF program were included in this study. At our center, ICSI was performed for male subfertility diagnosis, previous failed fertilization, or if the percentage of motile sperm in the inseminant was <85% after motile sperm isolation from the semen by density gradient centrifugation. We included both ICSI and standard insemination cycles in this study. Approximately, all embryo transfers are performed at the blastocyst stage of development; therefore, we excluded the cycles with day 3 embryo transfers to avoid this confounding factor. Oocyte banking for fertility preservation and cycles with donor oocytes were excluded.

Ovarian Stimulation in IVF

For all ovarian stimulation protocols, we require 2 lead ovarian follicles to be at least 18 mm in mean diameter, measured in 2 dimensions by transvaginal ultrasonography, to proceed with ovulation trigger using either 10,000 IU human chorionic gonadotropin, 2 mg leuprolide acetate, or the combination of 2 mg leuprolide acetate and 1,500 IU human chorionic gonadotropin given 36 hours before the planned oocyte retrieval.

Determination of Oocyte Maturity

After retrieval, oocyte maturity was assessed at 2 different time points, immediately at retrieval for all cycles and 6 hours later in the subset of patients having ICSI. Similar to the method used by Hammit et al. (7), immediately after retrieval the cumulus-oocyte complex was spread to evaluate the oocyte maturity on the basis of cumulus-coronal morphology and the presence of a polar body using phase-contrast microscopy under magnification, ×320. This observation takes <30 seconds and is conducted in a dish maintained on a heated stage. Embryologists classified oocytes as "MII" if they contained an extruded polar body and no signs of post maturity, and as "MI" in the absence of both an extruded polar body and germinal vesicle. Other classifications included germinal vesicle, postmature, and atretic oocytes. We have found that although it can sometimes be difficult to see a polar body through the cumulus cells at this time point, it is relatively easy to determine which eggs are either at the germinal vesicle stage or are postmature or atretic, thus differentiating these oocytes from MI or MII oocytes. Five experienced embryologists performed classification of oocytes.

In cycles using ICSI, oocyte maturity was assessed a second time after the cumulus was removed at the time of insemination, approximately 6 hours post retrieval. Classification of oocyte maturity at this time point was made by embryologists using the same criteria used for classification at retrieval.

Oocyte Maturity Ratio

Previous studies of oocyte maturity have only used ICSI cycles wherein oocyte maturity is assessed approximately 6 hours after the removal of cumulus cells (2, 8–10), and the oocyte maturity ratio is calculated as the ratio of MII oocytes to total oocytes retrieved (2). Because many oocytes mature in culture (3), in the subset of patients using ICSI for insemination, we compared 2 candidate definitions of oocyte maturity ratio at retrieval (MII oocytes at retrieval/ total oocytes retrieved and MI + MII oocytes at retrieval/ total oocytes retrieved) to determine which definition correlated best with the maturity ratio calculated at the time of ICSI. We determined the mean and standard deviation (SD) for oocyte maturity ratio and categorized maturity as high (>1 SD above the mean), average (mean ± 1 SD), below average (1–2 SD below the mean) and low (>2 SD below the mean).

Objective 1- Examine the Relationship between Oocyte Maturity Ratio and Live Birth and Other Outcomes of Interest

Our primary objective was to determine whether the oocyte maturity ratio is a predictor of live birth. Retrieval cycles were classified as resulting in live birth on the basis of the outcome from the first embryo transfer resulting from the retrieval cycle, whether that was a fresh or cryopreserved embryo transfer. Cycles that did not result in any transferable embryos were classified as no live birth. Other outcomes of interest investigated under this objective included clinical pregnancy, miscarriage, and fertilization rates after IVF. Clinical pregnancy was defined as the presence of a gestational sac and fetal heart rate on ultrasound examination, and for the clinical pregnancy rate, we included only the outcome from the first embryo transfer after oocyte retrieval. Fertilization rate was calculated by dividing the number of 2 pronuclei embryos (2PN) embryos by the total number of oocytes inseminated. In addition, we calculated the ratio of 2PN per total oocytes retrieved.

Objective 1 Statistical Analyses

We used Spearman's test to compare our 2 candidate definitions of oocyte maturity ratio at retrieval (MII oocytes at retrieval/ total oocytes retrieved and MI + MII oocytes at retrieval/total oocytes retrieved) and to determine which definition correlated best with the maturity ratio calculated at the time of ICSI. For this analysis, we included only the first ICSI cycle for each patient in the dataset. We applied the established criteria to interpret correlation coefficients, considering values of 0.60–0.80 to be moderately strong, and values >0.80 to be very strong (11). We then selected the definition of oocyte maturity ratio at retrieval that best correlated with the maturity ratio at ICSI and used that definition for all subsequent analyses to allow standard insemination cycles to be included in the sample.

We assessed the relationship between the oocyte maturity ratio and IVF outcomes by using generalized estimating equations to control for multiple cycles per patient. The IVF outcomes examined included clinical

TABLE 1

Cycle characteristics by insemination type

	All cycles (n = 1,451)	Standard insemination cycles (n = 648)	ICSI cycles (n = 803)	*P* value
Age (y)	34 ± 5	34 ± 4	33 ± 5	<.001
BMI	28.10 ± 6.81	28.10 ± 6.67	28.11 ± 6.92	.978
Diagnoses[a]				
Male factor	478 (32.9%)	52 (8.0%)	426 (53.1%)	<.001
Anovulation (including PCOS)	222 (15.3%)	109 (16.8%)	113 (14.1%)	.170
Diminished ovarian reserve (including advanced maternal age)	238 (16.4%)	108 (16.7%)	130 (16.2%)	.863
Endometriosis	177 (12.2%)	113 (17.4%)	64 (8.0%)	<.001
Tubal Factor	249 (17.2%)	144 (22.2%)	105 (13.1%)	<.001
Uterine Factor	50 (3.4%)	27 (4.2%)	23 (2.9%)	.227
Unexplained	355 (24.5%)	221 (34.1%)	134 (16.7%)	<.001
Other[b]	228 (15.7%)	88 (13.6%)	140 (17.4%)	.053
Smoking history	260 (17.9%)[c]	123 (19.0%)[c]	137 (17.1%)	.364
Oocyte maturity ratio at retrieval (MI+ MII oocytes at retrieval/ total oocytes retried)	85.5 ± 14.0	86.0 ± 14.4	85.2 ± 13.6	.256
Oocyte maturity ratio at retrieval (MII oocytes at retrieval/total oocytes retried)	47.4 ± 19.7	47.0 ± 20.2	47.7 ± 19.4	.484
Oocyte maturity ratio at ICSI (MII oocytes at ICSI/total oocytes retried)	—	—	79.4 ± 15.3	—

Note: Data presented as *n* (%) or mean ± SD. *P* values are for *t* tests or chi squared tests. BMI = body mass index, ICSI = Intracytoplasmic sperm injection, MI= metaphase I, MII = metaphase II, N/A = sample insufficient for statistic, PCOS = polycystic ovary syndrome.
[a] Participants may have had multiple diagnoses; the sum of category %s will not equal 100%.
[b] "other" includes recurrent pregnancy loss, genetic factors, cervical factor, use of a gestational carrier, single women, and same sex couples.
[c] Missing data for 2 cases.

Capper. Oocyte maturity predicts IVF outcomes. Fertil Steril 2022.

pregnancy, miscarriage, and fertilization rates. Patient age, use of preimplantation genetic testing, and number of embryos transferred were adjusted for use in multivariate models. Subgroup analyses were run for ICSI and standard insemination cycles.

A sensitivity analysis on the basis of number of autologous oocyte retrievals between January 2016 and July 2019 in our database found that with the assignment to 4 groups on the basis of maturity ratio, we would have 80% power to detect an absolute difference in live birth rate of 19.4% between the average and low maturity groups, 12.0% between the average and below average maturity groups, and 8.6% between the average and high maturity groups in a two-tailed chi-square and post hoc z-tests with alpha set to.05. We performed the sensitivity analysis in G*Power, assuming a live birth rate of 49.2% (2) for the average maturity group.

Objective 2- Examine Clinical Factors Associated with the Oocyte Maturity Ratio

Our secondary objective was to identify the clinical factors associated with oocyte maturity ratio. Independent factors assessed included age, diminished ovarian reserve, anovulation, total gonadotropins used, days of stimulation, trigger shot, and level of previous oocyte maturity ratio. Our dependent variable was oocyte maturity ratio, which was assessed as defined above. Given the smaller size of the subsample with 2 or more retrieval cycles, we categorized oocyte maturity ratios into 2 strata for our analysis of the relationship between maturity ratios across cycles. The strata included average to high maturity ratio (≥mean-1SD), and below average to low maturity ratio (<mean-1SD).

Objective 2 Statistical Analyses

We tested our hypothesis that the oocyte maturity ratio would be related to age, diminished ovarian reserve, anovulation, total gonadotropins used, and the trigger shot used with Spearman's test and *t* tests. We restricted these analyses to the first cycle in the dataset for each patient. To test our hypothesis that the oocyte maturity ratio would be related to the oocyte maturity ratio in previous cycles, we used Spearman's test and chi squares within the subsample of patients who had 2 or more retrieval cycles. This analysis was also conducted at a patient level.

All statistical analyses were performed in SPSS version 27 (IBM).

Ethics

The project was submitted to the University of Iowa Institutional Review Board for approval and qualified as exempt given the design involved data from an institutional review board approved database and the deidentified nature of the study (IRB #202002673).

RESULTS

In total, 1,451 IVF cycles (648 standard IVF and 803 ICSI) in 1,143 patients were included in the analysis representing

TABLE 2

Frequencies and outcomes of oocyte maturity groups.

Full sample		High (>99.5% mature) (n = 387)	Average (71.5–99.5% mature) (n = 850)	Below average (57.5–71.4% mature) (n = 161)	Low (<57.5% mature) (n = 53)
Live birth (%)	Frequency	152/375 (40.5)	423/811 (52.2)	74/155 (47.7)	15/52 (28.8)
	AOR	0.78 (0.60–1.00)	REF	0.87 (0.61–1.25)	0.41 (0.22–0.77)
Clinical pregnancy (%)	Frequency	183/375 (48.8)	494/813 (56.4)	88/156 (56.4)	16/52 (30.8)
	AOR	0.76 (0.59–0.98)	REF	0.88 (0.62–1.26)	0.32 (0.17–0.61)
Miscarriage (%)	Frequency	31/183 (16.9)	67/494 (13.6)	12/88 (13.6)	1/16 (6.3)
	AOR	0.96 (0.61–1.51)	REF	0.94 (0.51–1.75)	0.25 (0.03–1.91)
Fertilization rate	Mean	70.9 ± 24.4 (n = 384)	72.6 ± 17.8 (n = 842)	71.2 ± 21.9 (n = 157)	67.6 ± 25.9 (n = 50)
	ARR	0.99 (0.96–1.02)	REF	1.00 (0.96–1.03)	0.97 (0.91–1.04)
2PN per number retrieved	Mean	67.8 ± 24.3 (n = 384)	58.8 ± 16.0 (n = 843)	44.7 ± 14.9 (n = 157)	27.8 ± 14.1 (n = 52)
	ARR	1.10 (1.07–1.13)	REF	0.88(0.86–0.90)	0.75 (0.72–0.77)
ICSI Subsample		(n = 199)	(n = 484)	(n = 91)	(n = 4 29)
Live birth (%)	Frequency	79/193 (40.9)	253/457 (55.4)	43/88 (48.9)	10/28 (35.7)
	AOR	0.64 (0.45–0.90)	REF	0.83 (0.51–1.33)	0.52 (0.23–1.20)
Clinical pregnancy (%)	Frequency	96/193 (49.7)	290/458 (63.3)	54/89 (60.7)	10/28 (35.7)
	AOR	0.66 (0.46–0.93)	REF	0.97 (0.61–1.54)	0.38 (0.17–0.87)
Miscarriage (%)	Frequency	17/96 (17.7)	35/290 (12.1)	9/54 (16.7)	0/10 (0)
	AOR	1.48 (0.79–2.77)	REF	1.29 (0.57–2.92)	N/A
Fertilization rate	Mean	72.1 ± 19.6	73.7 ± 17.0	74.2 ± 19.7	62.8 ± 30.4
	ARR	0.99 (0.95–1.02)	REF	1.01 (0.97–1.05)	0.92 (0.83–1.02)
2PN per number retrieved	Mean	68.0 ± 22.8	58.8 ± 15.5	45.1 ± 13.6	27.8 ± 14.7
	ARR	1.10 (1.06–1.14)	REF	0.88 (0.85–0.90)	0.75 (0.72–0.79)
Standard insemination subsample		(n = 188)	(n = 366)	(n = 70)	(n = 24)
Live birth (%)	Frequency	73/182 (40.1)	170/354 (48.0)	31/67 (46.3)	5/24 (20.8)
	AOR	0.99 (0.68–1.44)	REF	0.94 (0.54–1.61)	0.29 (0.10–0.85)
Clinical pregnancy (%)	Frequency	87/182 (47.8)	204/355 (57.5)	34/67 (50.7)	6/24 (25.0)
	AOR	0.91 (0.63–1.33)	REF	0.77 (0.44–1.34)	0.26 (0.09–0.75)
Miscarriage (%)	Frequency	14/87 (16.1)	32/204 (15.7)	3/34 (8/8)	1/6 (16.7)
	AOR	0.77 (0.38–1.56)	REF	0.50 (0.16–1.55)	1.12 (0.14–9.36)
Fertilization rate	Mean	69.6 ± 25.8	71.1 ± 18.7	67.5 ± 24.0	74.2 ± 16.4
	ARR	1.00 (0.96–1.04)	REF	0.97 (0.93–1.03)	1.04 (0.97–1.12)
2PN per number retrieved	Mean	67.6 ± 25.8	58.9 ± 16.7	44.1 ± 15.8	27.7 ± 13.5
	ARR	1.10 (1.06–1.15)	REF	0.87 (0.84–0.90)	0.74 (0.71–0.78)

Note: Values are presented as frequency (percentage) or mean ± SD. Factors adjusted for in AOR and ARR include: patient age, use of preimplantation genetic testing, and number of embryos transferred. AOR = Adjusted odds ratio, ARR = adjusted rate ratio, ICSI = intracytoplasmic sperm injection, N/A = sample insufficient for statistic, 2PN = 2 pronuclei embryos, REF = referent.

Capper. Oocyte maturity predicts IVF outcomes. Fertil Steril 2022.

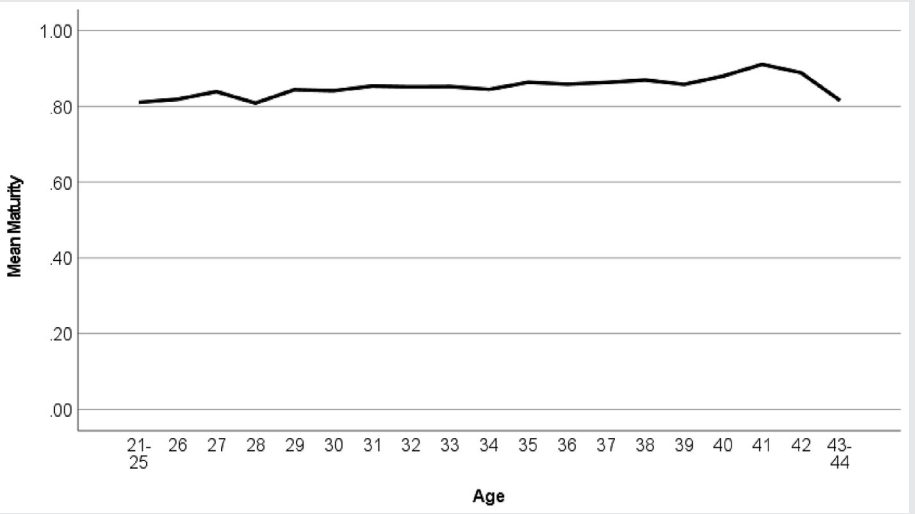
22,629 oocytes and 12,980 embryos. Among the 211 patients with multiple cycles in the dataset, 101 (47.9%) had multiple ICSI cycles, 71 (33.6%) had multiple standard IVF cycles, and 39 (18.5%) had both standard IVF and ICSI cycles. Maternal age at cycle start ranged from 21–44 years with an average of 34 ± 5 years. Diagnostic demographic data are shown in Table 1.

When comparing the oocyte maturity ratio at the 2 time points, among the 629 initial ICSI cycles, there was strong correlation between MI + MII oocytes at retrieval per total oocytes and MII oocytes at ICSI per total oocytes (Spearman's rank correlation (r_s) = 0.84, $P<.001$). The mean difference in maturity ratio at retrieval calculated by <E>(MI + MII)/total oocytes retrieved to maturity ratio at ICSI (MII/total oocytes retrieved)<e> was 5.8% ± 8.3% SD. In contrast, there was poor correlation with MII oocytes at retrieval per total oocytes and MII oocytes at ICSI per total oocytes (r_s = 0.44; $P\leq.001$). For subsequent analyses, we used the definition of oocyte maturity ratio MI + MII at retrieval per total oocytes as our measure of maturity; therefore, we could include all cycles (both ICSI and standard insemination cycles). Four maturity ratio strata were defined as described above on the basis of a mean maturity ratio of 85.5 ± 14.0 SD. The resulting 4 groups were as follows: high (> 99.5% mature, n = 387), average (71.5%–99.5% mature, n = 850) below average (57.5%–71.4% mature, n = 161), and low (<57.5% mature, n = 53).

Objective 1- Examine the Relationship Between Oocyte Maturity Ratio and Live Birth and Other Outcomes of Interest

The effect of oocyte maturity ratio on the live birth, clinical pregnancy, miscarriage, and the fertilization rates are shown in Table 2. After adjusting for age, preimplantation genetic testing, and number of embryos transferred, we found that a low oocyte maturity ratio was associated with a decreased live birth rate (AOR, 0.41; 95% CI, 0.22–0.77) and clinical pregnancy rate (AOR, 0.32; 95% CI, 0.17–0.61). We did not find a relationship between oocyte maturity and miscarriage rate or fertilization rate (Table 2). The number of 2PN embryos per retrieved oocyte was found to be associated with the

FIGURE 1



Mean oocyte maturity ratios in the first cycle by a woman's age represented by a solid black line — on the plot.

Capper. Oocyte maturity predicts IVF outcomes. Fertil Steril 2022.

maturity ratio at retrieval with high (AOR, 1.10; 95% CI, 1.07–1.13), below average (AOR, 0.88; 95% CI, 0.86–0.90), and low maturity (AOR, 0.75; 95% CI, 0.72–0.77) groups, all differing from average.

Objective 2- Examine Clinical Factors Associated with the Oocyte Maturity Ratio

Women with anovulation had a slightly reduced oocyte maturity ratio (81.9 ± 14.9 vs. 85.5 ± 14.0, P=.002) compared with women in other diagnostic categories, whereas women with diminished ovarian reserve had a slightly increased oocyte maturity ratio (87.8 ± 18.2 vs. 84.5 ± 13.5, P=.034). Clinical factors that were not associated with oocyte maturity ratios included woman's age (Fig. 1) (r_s = 0.15; P≤.001), days of stimulation before trigger (r_s = 0.08; P=.006), type of trigger (Fig. 2), and total gonadotropins used (r_s =0.15; P<.001).

When oocyte maturity ratio was compared between cycles as a continuous variable, there was minimal correlation (r_s =0.31; P≤.001) within the subsample who had 2 or more cycles (n = 211). However, when assessed categorically, a relationship was found between oocyte maturity across cycles, with 34% of those classified as having a below average to low oocyte maturity ratio (<71.4% mature) in their first cycle also classified as having a below average to low oocyte maturity ratio in their second cycle. In contrast, only 9% of cycles classified as having an average to optimal oocyte maturity ratio (>71.5% mature) in their first cycle were classified as having a below average to low oocyte maturity ratio in their second cycle (P=.002).

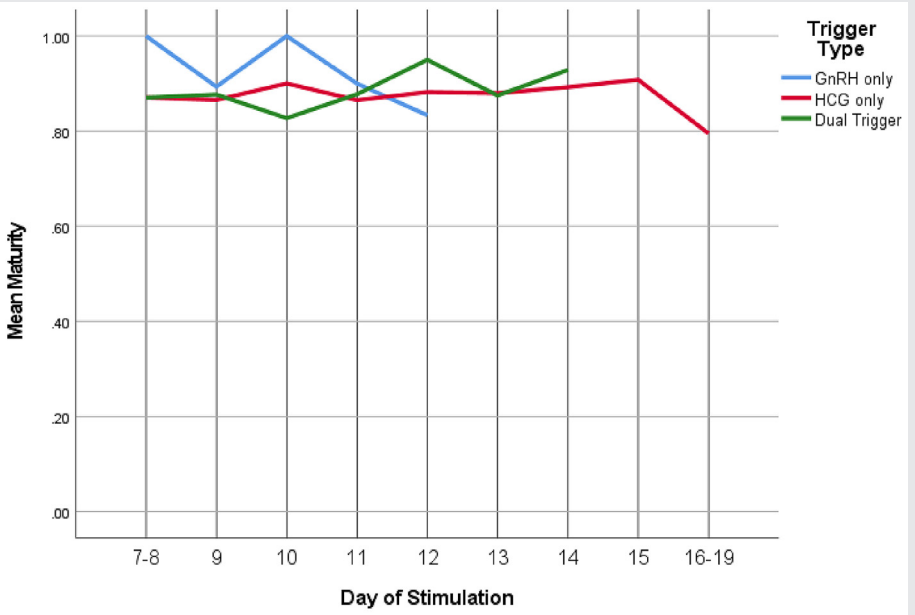
DISCUSSION

The primary objective of our study was to determine whether a low oocyte maturity ratio, among the cohort of oocytes retrieved, was a predictor of poor outcomes in IVF. We found that cycles classified as having a poor oocyte maturity ratio (<57.5% of oocytes reaching the MI or MII stage of development immediately after retrieval) had significantly lower live birth and clinical pregnancy rates than cycles with high oocyte maturity ratios. In addition, the total number of fertilized oocytes (2PN embryos) per total number of oocytes retrieved declined with the low oocyte maturity ratios. Although the fertilization rate per mature oocyte was the same in all groups, the clinical outcome was poor when the oocyte maturity ratio was low. Surprisingly, a high oocyte maturity ratio was associated with a slightly lower live birth rate compared with an average oocyte maturity ratio in women, although this association did not reach statistical significance in our study. The reason for this is unclear, but suggests the potential for a more complex relationship between maturity and clinical outcomes.

When evaluating multiple cycles in the same woman, there was a tendency for low oocyte maturity ratio to be repetitive. Although low oocyte maturity ratio often increased in the subsequent cycles, it was relatively rare for women with optimal or average oocyte maturity ratios to have below average to low oocyte maturity ratios in their second cycles. The finding of repetitively low oocyte maturity suggests the possibility that in some women defects in oocyte maturation and meiosis could be a cause of infertility and repetitive failed IVF cycles.

Our secondary objective was to identify the factors predictive of low oocyte maturity ratios. Moreover, the factors that have been hypothesized to impact oocyte maturity include patient age, the diagnosis of anovulation, diagnosis of diminished ovarian reserve, and number of ovarian stimulation days in an IVF cycle (2, 8, 9, 12–15). In addition to these factors, we looked at the relationship between the total dosage of gonadotropins used in a cycle on oocyte maturity. We

FIGURE 2



Mean oocyte maturity ratios by days of stimulation and type of trigger shot. GnRH = gonadotropin releasing hormone, hCG = human chorionic gonadotropin. Trigger types are differentiated by *blue* (GnRH), *red* (hCG), and *green* (dual) lines on the plot.

Capper. Oocyte maturity predicts IVF outcomes. Fertil Steril 2022.

found that women with anovulation had a slightly reduced oocyte maturity ratio and women with diminished ovarian reserve had a slightly increased oocyte maturity ratio compared with all other diagnoses. None of the other factors studied had a significant association ($P<.05$ or $r_s>0.60$) with the oocyte maturity ratio.

Previous studies of oocyte maturity in IVF cycles have mostly been performed in ICSI cycles. As such, generalizability of findings of the relationship between oocyte maturity and IVF outcomes is limited. More studies of oocyte maturity in regular insemination cycles are needed to expand the knowledge of impacts of oocyte maturity on outcomes in non ICSI cycles. When conducting further studies on oocyte maturity, it is important to consider the definitions of oocyte maturity, which would allow comparability of findings from studies performed in ICSI and regular insemination cycles. Studies performed in ICSI cycles have generally used a definition of oocyte maturity which is based on the assessment of maturity when the cumulus cells have been stripped from the oocyte (2, 8–10). Because many oocytes mature in culture (3), the assessment of MII oocytes at retrieval and after removal of cumulus cells, 6 hours later, will not yield inherently comparable measures of oocyte maturity. We attempted to address this issue by considering inclusion of MI oocytes at retrieval in the maturity ratio along with MII oocytes to account for the 6 additional hours that the oocytes have to mature in culture in cycles which assess maturity after removal of cumulus. We found that our oocyte maturity ratio definition, which included both MI and MII oocytes at this earlier time point, correlated better with the ratio of MII oocytes after removal of cumulus 6 hours later in the subset of patients having ICSI than with a ratio including only MII oocytes at retrieval. This is likely because of a combination of oocytes maturing in culture and the embryologist's inability to observe a polar body when the oocyte was surrounded by cumulus cells. Further study is needed to validate an appropriate measure of oocyte maturity which will allow comparison of findings from studies conducted in ICSI and regular insemination cycles.

Despite the differences in study design, our findings agree with previous studies showing a reduced pregnancy rate in cycles with low oocyte maturity ratios (2, 10). Future studies should focus on the cumulative pregnancy rate as our finding of fewer embryos in cycles with lower oocyte maturity ratios would likely have an even greater detrimental effect on this outcome.

Interestingly, our study confirmed a lack of a strong correlation between oocyte maturity and age (2, 9, 12). Age may not affect the underlying cytoplasmic and nuclear maturation during meiosis as observed under a microscope at least. Additionally, our study confirmed a lack of a strong correlation between oocyte maturity and number of stimulation days (2). This is surprising because in clinical practice, longer stimulations are often used in an attempt to recruit more mature oocytes. We also found that the dose of gonadotropins and the trigger shot used did not seem to affect the oocyte maturity ratios suggesting that we may be limited in our ability to influence oocyte maturity effectively with the current protocols used for ovarian stimulation. Contrary to the finding of a smaller study that anovulation did not influence oocyte quality, our study demonstrated a relationship between anovulation diagnosis and oocyte maturity rates (14).

Limitations of our study include the retrospective evaluation of prospectively collected data and that the potentially important and yet unknown variables affecting oocyte maturity were not captured in the database. Because oocyte maturity ratios are not normally distributed, our groups of maturity ratios were skewed from the expected group sizes for normally distributed data. The choice to divide groups using standard deviations was an a priori decision in the study design. In addition, we were unable to report interobserver and intraobserver variabilities for classification of oocytes, as these parameters are not assessed in our institution's quality control program. The lack of standardized time points and definitions for determining oocyte maturity make comparisons with prior studies and with individual IVF labs challenging. It should also be noted that although we routinely assess oocyte maturity in all cases after retrieval; however, many labs do not assess the oocyte maturity, especially if they are doing a high rate of ICSI insemination cycles. As a result, each laboratory will need to gain experience and establish norms before incorporating oocyte maturity as a cycle quality measure for their patient population.

Nevertheless, our study adds to the literature by including standard insemination cycles. Our findings suggest that patients with low oocyte maturity ratio have poor IVF outcomes, including decreased pregnancy and live birth rates–information that can be used to counsel some patients who have had a failed cycle. Fortunately, low oocyte maturity ratios are uncommon and when present in the first cycle are often not present in subsequent cycles, although in some patients it is a repetitive finding. We found no strong evidence that differences in ovarian stimulation length, gonadotropin dose, or type of trigger shot influence the maturity ratio. Further research is required to discover modifiable factors that may improve oocyte maturity.

DIALOG: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/34062

REFERENCES

1. Rita de Cássia SF, Braga DP, Semiao-Francisco L, Madaschi C, Iaconelli A Jr, Borges E Jr. Metaphase II human oocyte morphology: contributing factors and effects on fertilization potential and embryo developmental ability in ICSI cycles. Fertil Steril 2010;94:1115–7.
2. Parrella A, Irani M, Keating D, Chow S, Rosenwaks Z, Palermo GD. High proportion of immature oocytes in a cohort reduces fertilization, embryo development, pregnancy and live birth rates following ICSI. Reprod Biomed Online 2019;39:580–7.
3. Paes VM, de Figueiredo JR, Ryan PL, Willard ST, Feugang JM. Comparative analysis of porcine follicular fluid proteomes of small and large ovarian follicles. Biology (Basel) 2020;9.
4. Palermo GD, Cohen J, Rosenwaks Z. Intracytoplasmic sperm injection: a powerful tool to overcome fertilization failure. Fertil Steril 1996;65:899–908.
5. Lee HJ, Jee BC, Suh CS, Kim SH, Moon SY. Oocyte maturity in relation to woman's age in in vitro fertilization cycles stimulated by single regimen. Yonsei Med J 2012;53:181–5.
6. Swain JE, Pool TB. ART failure: oocyte contributions to unsuccessful fertilization. Hum Reprod Update 2008;14:431–46.
7. Hammitt DG, Syrop CH, Van Voorhis BJ, Walker DL, Miller TM, Barud KM, et al. Prediction of nuclear maturity from cumulus-coronal morphology: influence of embryologist experience. J Assist Reprod Genet 1992;9:439–46.
8. Pereira N, Neri QV, Lekovich JP, Palermo GD, Rosenwaks Z. The role of in-vivo and in-vitro maturation time on ooplasmic dysmaturity. Reprod Biomed Online 2016;32:401–6.
9. Halvaei I, Ali Khalili M, Razi MH, Nottola SA. The effect of immature oocytes quantity on the rates of oocytes maturity and morphology, fertilization, and embryo development in ICSI cycles. J Assist Reprod Genet 2012;29:803–10.
10. Ozgur K, Bulut H, Berkkanoglu M, Coetzee K, Ay S. Oocyte maturation-index as measure of oocyte cohort quality; a retrospective analysis of 3135 ICSI cycles. Middle East Fertil Soc J 2015;20:37–42.
11. Chan YH. Biostatistics 104: correlational analysis. Singapore Med J 2003;44:614–9.
12. Grøndahl ML, Christiansen SL, Kesmodel US, Agerholm IE, Lemmen JG, Lundstrøm P, et al. Effect of women's age on embryo morphology, cleavage rate and competence-A multicenter cohort study. PloS One 2017;12:e0172456.
13. Keefe D, Kumar M, Kalmbach K. Oocyte competency is the key to embryo potential. Fertil Steril 2015;103:317–22.
14. Nikbakht R, Mohammadjafari R, Rajabalipour M, Moghadam MT. Evaluation of oocyte quality in polycystic ovary syndrome patients undergoing ART cycles. Fertil Res Pract 2021;7:2.
15. Azziz R, Carmina E, Chen Z, Dunaif A, Laven J, Legro R, et al. Polycystic ovary syndrome. Nat Rev Dis Primers 2016;2:16057.

La baja tasa de madurez de ovocitos se asocia con una reducción de la tasa de nacidos vivos en fecundacion in vitro e inyección intracitoplasmática de espermatozoides.

Objetivo: Determinar si la baja tasa de madurez ovocitaria en una cohorte de ovocitos de un ciclo de fecundación in vitro predice los resultados y examinar los factores clínicos asociados con la madurez del ovocito.

Diseño: Un estudio de cohorte retrospectivo.

Lugar: Un centro médico académico.

Intervención(es): Determinación de la madurez del ovocito inmediatamente después de la extracción y 6 horas después si se realizó inyección intracitoplasmática de espermatozoides.

Medida(s) de resultado principal: el resultado primario fue la tasa de nacidos vivos después de la primera transferencia de embriones. Los resultados secundarios incluyeron tasas de embarazo clínico, aborto espontáneo y fertilización.

Resultado(s): Después de ajustar la edad, estudio genético preimplantacional y la cantidad de embriones transferidos, encontramos que una proporción baja de madurez de ovocitos se asoció con una tasa de nacidos vivos reducida (odds ratio ajustada [AOR], 0.41; 95 % intervalo de confianza [IC], 0.22– 0.77) y tasa de embarazo clínico (AOR, 0.32; IC 95 %, 0.17–0.61). No encontramos una relación entre la madurez del ovocito y la tasa de abortos espontáneos (AOR, 0.25; IC 95 %, 0.03–1.91) o la tasa de fecundación (prueba de Welch). Se encontró que el número de embriones de 2 pronúcleos por ovocito recuperado estaba asociado con la relación de madurez en la recuperación. Las pacientes con anovulación tenían una madurez de los ovocitos ligeramente reducida en comparación con otros grupos de diagnóstico.

Conclusión(es): La baja tasa de madurez de los ovocitos es un factor importante relacionado con los resultados deficientes de la fertilización in vitro, incluida la disminución de las tasas de embarazo y de nacidos vivos.