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Factors inducing decreased oocyte maturation rate: a retrospective analysis of 20,939 ICSI cycles

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Abstract

Purpose Decreased oocyte maturation rate (OMR) is associated with worse clinical outcomes in IVF/ICSI cycles. The clinical features inducing decreased OMR remain unknown. The study is designed to explore the factors influencing the incidence of decreased OMR and its effects on clinical outcomes.

Methods This is a retrospective case–control study analyzing data from 20,939 ICSI cycles in a reproductive center of university affiliated hospital from January 2015 to December 2017. Patients with a decreased OMR (< 30%) were characterized as Group A and those with an OMR ≥ 30% constituted Group B. Candidate factors of decreased OMR and clinical outcomes were compared between the two groups.

Results There were 1.3% cycles with an OMR < 30% and 22.16% of all oocytes retrieved (12.87 per cycle in average) were immature. Primary infertility, longer duration of infertility, larger BMI, more previous assisted reproductive times, less oocytes retrieved were risk factors for decreased OMR. Compared with long agonist protocol, patients received antagonist protocol for COH had a higher incidence of decreased OMR. The fertilization rate and subsequent embryo development of oocytes in Group A were worse than Group B. Implantation rate and clinical pregnancy rate were both lower in Group A than Group B.

Conclusion Primary infertility, duration of infertility, BMI, previous assisted reproductive times, number of oocytes retrieved and COH protocol were found to be factors inducing decreased OMR. Patients with decreased OMR had worse clinical outcomes.

Keywords Oocyte maturation · ICSI · Risk factor · Pregnancy

Introduction

Mature oocyte is integrant for a successful pregnancy. In the human ovary, oocytes arrest in diplotene stage of meiosis I since fetal life. Only those in fully grown follicles received stimulation of LH surge resume meiotic process. Their nuclei–germinal vesicles (GV) break down and progress to GVBD (germinal vesicle breakdown) stage, about 24 h after which, the oocyte will exclude the first polar body and be arrested at metaphase II (MII) phase, ready for fertilization [1, 2].

In vitro fertilization (IVF) helps to shed light on the regulation of oocyte maturation by controlled ovarian hyperstimulation (COH). During the COH procedure, exogenous hormones were administrated to promote the growth of follicles and to induce more than one mature oocyte [3]. By the time of retrieval, oocytes were supposed to be picked up at MII phase, being competent to be fertilized normally. However,

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unwanted immature oocytes usually show up because of developmental unsynchronization.

Upon retrieval, oocytes would be classified as GV, MI, or MII as a consequence of evaluating the morphologic mature marks, mostly including the appearance of nucleus and the existence of polar body [4]. Oocytes that have not progressed through meiosis to MII stage are considered to be immature and incompetent to be fertilized. At least one immature oocyte was produced in 8.6–15.2% of all infertile women as reported [5]. In the study of Halvaei et al. [6], 15% of all retrieved oocytes remained immature. Successful fertilization with clinical pregnancy would be greatly reduced if the oocyte maturation rate (OMR) were lower than 75% [7]. The data were scarce and old and regrettably, no literature has been published to report the definition, affecting factors of decreased OMR and its relationship with IVF outcomes.

In clinical practice, we found that an OMR lower than 30% severely reduce success chance of IVF for infertile patients. Thus, we retrospectively analyze the data of ICSI cycle to discover the possible factors inducing decreased oocyte maturation rate and its influence on clinical outcomes. Within the findings, clinicians may gain some insight to improve the strategy for patients who might produce a large proportion of immature oocytes.

Materials and methods

Data from ICSI cycles performed in the Reproductive Medicine Center of Peking University Third Hospital from January 2015 to December 2017 were collected. This study was approved by the institutional review board of Peking University Third Hospital and all patients signed informed consents.

Only cycles with maturity evaluation of oocytes were included. The exclusion criteria were as following: IVM cycle, PGD cycle, retrieved oocytes less than 4, female abnormal chromosomal karyotype. Oocyte maturation rate was calculated as the ratio of mature oocyte number over retrieved oocyte number in the same cycle. Patients with a maturation rate less than 30% were assigned to Group A (decreased maturation rate group). Those with the rate $\geq$ 30% constitute Group B (normal maturation rate group).

Data collected included age, type of infertility, body mass index (BMI), duration of infertility, previous assisted reproductive times, previous pregnancy times, basal and HCG day gonadal hormone levels, antral follicle count (AFC) and cycle outcomes. Patients were scheduled for oocyte retrieval 34–36 h after the hCG injection. Indications and techniques for oocyte aspiration, oocyte and embryo culture, insemination, intracytoplasmic sperm injection and embryo transfer were based on the routine of the center. To confirm the early pregnancy, serum hCG was measured 13 days after the cleavage embryo transfer or 11 days after the blastocyst transfer. Ultrasound scan was performed 30–35 days after embryo transfer. An intrauterine clinical pregnancy was defined as the presence of a gestational sac with fetal heart activity in the uterine cavity.

Statistical analysis was performed using Statistical Package for Social Science (SPSS) software, version 25.0 (IBM, Armonk, New York, USA). The results were analyzed using univariate logistic regression analysis. Comparisons between ratios were performed using the Chi-square test. The Mann–Whitney *U* test was used when appropriate. A multivariate logistic regression analysis was used to estimate the risk factors on decreased oocyte maturation rate. All reported *P* values were two-tailed, and $P < 0.05$ was established as the level of significance.

Results

There were 20,939 fresh ICSI cycles in our center from 2015 to 2017. Thereinto, 4869 cycles were excluded for following reasons: IVM cycle (237), PGD cycle (2197), retrieved oocytes less than 4 (2069), abnormal chromosomal karyotype (114), frozen–thawed oocyte cycle (93) and deficient data (159). Finally, 16,070 cycles were included for analysis. There were 210 cycles (1.3%) with an OMR < 30% (Group A) and 15,860 others with an OMR $\geq$ 30% (Group B). Of all 206,851 oocytes retrieved (12.87 per cycle in average), 22.16% (45,831) were immature.

The patients and cycle characteristics by maturation rate are summarized in Table 1. A total of 19 candidate variables were tested by univariate analysis. Eleven factors were identified as being possibly significantly different between the two groups ($P < 0.10$): female age, type of infertility, duration of infertility, BMI, previous assisted reproductive times, previous pregnancy times, antral follicle count (AFC), stimulation protocol, E2 level in HCG day, dosage of gonadotropin and number of oocytes retrieved (Table 1).

These 11 variables were next involved in a multivariate logistic regression analysis model to explore potential confounding factors. The results showed that female age, previous pregnancy times, AFC, E2 level in HCG day and dosage of gonadotropin were not responsible for decreased oocyte maturation rate. Instead, primary infertility, duration of infertility, BMI, previous assisted reproductive times were independent risk factors for decreased oocyte maturation rate. Number of oocytes retrieved is a possible protective factor of decreased maturation rate [$P = 0.000$; odds ratio (OR) 0.947; 95% confidence interval (CI) 0.920–0.974]. Compared with long agonist protocol, patients received antagonist protocol for COH had a higher incidence of decreased OMR ($P = 0.038$; OR 2.039; 95% CI 1.314–3.163) while those got prolong agonist protocol, short agonist

Table 1 Univariate analysis of factors influencing oocyte maturation rate

Variable	Decreased maturation rate ($n=210$)	Normal maturation rate ($n=15,860$)	P
Age, years	33.77 ± 5.10	32.25 ± 4.94	0.000[a]
Type of infertility, no. (%)			
Primary	154 (73.33)	10,731 (67.66)	0.082[b]
Secondary	66 (26.67)	5129 (32.34)	
Duration of infertility, years	5.55 ± 3.72	4.73 ± 3.64	0.001[a]
BMI, kg/m^2	23.42 ± 4.60	22.53 ± 3.34	0.000[a]
Previous assisted reproductive times	1.05 ± 1.29	0.70 ± 1.27	0.000[a]
Previous pregnancy times	0.37 ± 0.844	0.47 ± 0.91	0.099[a]
Basal FSH, IU/L	6.70 ± 3.59	6.22 ± 9.60	0.524[a]
Basal LH, IU/L	6.27 ± 38.28	4.10 ± 52.30	0.622[a]
Basal E2, pmol/L	159.55 ± 82.22	163.43 ± 158.65	0.735[a]
Basal P, nmol/L	1.33 ± 1.07	1.44 ± 5.56	0.807[a]
AMH, ng/ml	2.83 ± 3.63	3.58 ± 3.09	0.239[a]
AFC	10.76 ± 6.79	11.62 ± 5.74	0.054[a]
Stimulation protocol, no. (%)			
Antagonist	130 (61.90)	8856 (55.84)	0.001[b]
Prolong agonist	19 (9.05)	1382 (8.71)	
Short agonist	14 (6.67)	758 (4.78)	
Mild-stimulation	3 (1.43)	35 (0.22)	
Long agonist	44 (20.95)	4829 (30.45)	
E2 of HCG day, pmol/L	7791.02 ± 10,098.64	9259.31 ± 6038.53	0.000[a]
LH of HCG day, IU/L	2.30 ± 2.96	1.94 ± 2.33	0.085[a]
P of HCG day, nmol/L	2.63 ± 1.594	2.81 ± 1.65	0.119[a]
Duration of stimulation, days	10.91 ± 2.65	11.06 ± 2.27	0.357[a]
Dosage of Gn, IU	2819.26 ± 1343.04	2591.20 ± 1172.50	0.006[a]
No. of oocytes retrieved	10.53 ± 7.51	12.90 ± 7.00	0.000[a]

Numbers are mean ± SD unless otherwise indicated

No. number, *AFC* antral follicle count, *Gn* gonadotropin

[a]Univariate logistic regression analysis

[b]Chi-square test

protocol or mild-stimulation protocol showed no significant difference in the incidence of decreased OMR (Table 2).

As for ICSI outcomes shown in Table 3, patients in Group A had less fertilized oocytes (1.14 ± 1.36 vs 6.55 ± 4.46) and significantly lower fertilization rate (53.43% ± 42.50% vs 63.97% ± 23.47%) than those in Group B ($P=0.000$, 0.043, respectively). Number of cleavage embryo and cleavage rate were also lower in Group A. As a consequence, women in Group A had significantly less available and top-quality embryos and showed lower available and top-quality embryo rates.

Endometrial thickness in HCG day is similar between the two groups but more patients in Group A chose to cancel the transfer cycle than Group B (53.33% vs 27.13%, $P=0.000$).

Table 2 Multivariate logistic regression analysis of factors on decreased oocyte maturation rate

Variable	β	Wald	P	OR (95% CI)
Infertility type (primary vs. secondary)	0.417	5.354	0.021	1.517 (1.066, 2.160)
Duration of infertility	0.042	4.787	0.029	1.042 (1.004, 1.082)
BMI	0.078	13.786	0.000	1.081 (1.038, 1.127)
Previous assisted reproductive times	0.107	4.250	0.039	1.113 (1.005, 1.232)
No. of oocytes retrieved	− 0.055	14.169	0.000	0.947 (0.920, 0.974)
Stimulation protocol (a vs. b)	0.712	4.311	0.038	2.039 (1.314, 3.163)

β regression coefficient, *OR* odd ratio, *a* antagonist protocol, *b* long agonist protocol

Table 3 Comparison of outcomes between the two groups

Outcome	Group A	Group B	*P*
No. of fertilized oocyte	1.14 ± 1.36	6.55 ± 4.46	0.000[a]
Fertilization rate (%)	53.43 ± 42.50	63.97 ± 23.47	0.043[a]
No. of cleavage embryo	1.42 ± 1.36	7.41 ± 4.76	0.000[a]
Cleavage rate (%)	67.88 ± 39.50	72.63 ± 21.67	0.011[a]
No. of embryos available	0.85 ± 1.07	4.95 ± 3.90	0.000[a]
Available embryo rate (%)	42.54 ± 43.36	48.68 ± 25.02	0.000[a]
No. of top-quality embryo	0.56 ± 1.00	4.17 ± 3.83	0.002[a]
Top-quality embryo rate (%)	26.76 ± 40.33	40.88 ± 28.13	0.000[a]
Endometrial thickness (mm)	10.74 ± 1.85	10.96 ± 1.68	0.056[a]
Cycle cancel rate	53.33% (112/210)	27.13% (4291/15,860)	0.000[b]
No. of embryo transferred	1.34 ± 0.48	1.88 ± 0.33	0.000[a]
Implantation rate	16.69% (22/131)	26.45% (5748/21,731)	0.000[b]
Clinical pregnancy rate			
Per OPU cycle	9.52% (20/210)	28.51% (4522/15,860)	0.000[b]
Per ET cycle	20.41% (20/98)	39.09% (4522/11,569)	0.000[b]
Ectopic pregnancy rate	0 (0/98)	0.97% (112/11,569)	1.000[b]
Multiple pregnancy rate	10.00% (2/20)	26.89% (1216/4522)	0.089[b]
Abortion rate	15.00% (3/20)	12.61% (570/4522)	0.733[b]

Numbers are mean ± SD unless otherwise indicated

No. number, *OPU* ovum pick up, *ET* embryo transfer

[a]Mann–Whitney U test

[b]Chi-square test

As for those (98 in Group A and 11,569 in Group B) had fresh embryos transferred, less embryos were transferred in Group A (1.34 ± 0.48 vs 1.88 ± 0.33, $P = 0.000$) and lower implantation rate was found in Group as well (16.69% vs 26.45%, $P = 0.000$). Thus, clinical pregnancy rates, both per OPU cycle (9.52% vs 28.51%, $P = 0.000$) and per ET cycle (20.41% vs 39.09%, $P = 0.000$), were significantly lower in Group A than Group B. Ectopic pregnancy rate, multiple pregnancy rate and abortion rate were shown to be similar between the two groups (Table 3).

Discussion

Beall et al. [5] put forward a concept of "the syndrome of oocyte maturation failure", meaning repeated production of a majority of immature oocytes. The syndrome would reduce the success rate of IVF attempt as the number of available oocyte was diminished. However, the definition of "majority" was not given. In the present study, we described decreased oocyte maturation rate as lower than 30% according to our clinical experience, waiting for more studies to validate or correct it. Within this definition, the incidence of decrease OMR was 1.3% (210/16,070) among cycles included. After being analyzed with univariate analysis and multivariate logistic regression analysis, 6 of 19 candidate variables were found to be factors affecting the incidence of decrease OMR.

Primary infertility, duration of infertility, BMI, previous assisted reproductive times were indicated to be risk factors for decreased OMR. Primary infertility was characterized as the clinical feature of oocyte maturation failure [5]. Together with longer duration of infertility, larger BMI and more previous assisted reproductive times, they represent a greater severity of infertility. These factors could be implied by previous studies to be related to decreased OMR. A case of oocyte maturation block was reported from a 34-year-old female with a history of 14 years of primary infertility and four times of IUI failure [8]. Levran et al. [9] reported eight cases of oocyte maturation arrest, patients of which aged 25–35 years and failed at least six cycles of assisted reproduction. The average infertile duration was 8.2 years and six of them presented with primary infertility. The study of Hourvitz et al. [10] included two patients with repeated GV oocyte arrest and both of them had 7-year primary infertility and at least three failed IVF attempts. Gulekli et al. [11] reported two patients with repeated oocyte maturation arrest and they had a history of 5/10 years of primary infertility and at least three times of IVF failure.

Number of oocytes retrieved is shown to be a possible protective factor of decreased maturation rate in our study. Women in Group B retrieved more oocytes than those in Group A (12.90 ± 7.00 vs 10.53 ± 7.51,

$P = 0.000$). The result was consistent with Griffin et al. [12], reporting more oocytes retrieved (9 vs 7) when OMR was improved by dual trigger. However, Avrech et al. [13] found that cycles with at least one immature oocyte had more retrieved oocytes than cycles with all oocytes mature (9.2 ± 0.6 vs 7.9 ± 0.2, $P = 0.02$). More research are needed to clarify the correlation between number of oocytes retrieved and oocyte maturation rate.

Patients received antagonist protocol had a higher incidence of decreased OMR comparing with long agonist protocol as shown in the results. In our center, antagonist protocol were mainly used on patients with high ovarian response, who often produce proportionately more immature oocytes without known reasons as reported by Sachs et al. [14]. In addition, hCG was administrated for the trigger in our antagonist protocol. However, it was suggested that the percentage of immature oocytes retrieved was higher when triggered with hCG compared with GnRH agonist [15]. This may be something we could discuss to improve clinical practice.

The etiology of decrease in OMR may also partially lie on genetic features. For example, mutations of TUBB8 has been found to be responsible for human oocyte maturation arrest. Recently, more and more genes related to oocyte growth, maturation and fertilization have been reported in animal models [5]. However, similar exploration on human oocyte usually fails to discover inspiring results because of the complicated phenotypes of human and its difference with animal phenotypes. In the present study, we focus on discussing clinical features that may induce decrease in OMR.

Comparing clinical outcomes, patients with decreased OMR performed worse in fertilization and subsequent embryo development. Implantation rate and clinical pregnancy rate were also significantly lower in Group A. It is easy to understand as less embryos were available for transfer and the quality of mature oocytes of these patients might be poorer than those of Group B. Previous study reported that no pregnancy was achieved when the OMR was lower than 75%. To increase IVF success rate of women with decreased OMR, in vitro maturation (IVM) can be an attempt to get mature oocytes from immature ones. Nevertheless, poor maturation rate, significantly lower pregnancy rate than routine IVF cycle and the worry about safety of oocytes matured in vitro remind clinicians to treat the application of IVM with caution [16]. There are other methods reporting to improve oocyte maturation rate and clinical outcomes. For patients with a history of more than 25% immature oocytes retrieved, double trigger with GnRH agonist and hCG increased oocyte maturation rate from 38.5 to 75.0% [12]. Extending the interval between hCG administration and oocyte retrieval could significantly improve the maturation rate and pregnancy rate of patients with a history of less than 50% mature oocytes retrieved [17, 18]. None of the alterations have been proven to be effective and more studies are required.

This is the first study exploring the possible factors inducing decreased oocyte maturation rate, the definition of which has not been given before. The negative effects of decreased OMR on clinical outcomes of ICSI cycle are also discovered. These findings can provide clinical practitioners with reference to predict the incidence of decreased OMR and generate strategy accordingly. For example, dual trigger with GnRH agonist and hCG might improve oocyte maturation rate [12, 19]. This study also helps to find future research directions to study more about oocyte maturation. The large sample size and strict exclusion criteria constitute the strengths of the article. However, the study is limited by its retrospective design and confounding factors including different types of stimulation and ovulation induction drugs. The cut-off value of 30% for decreased OMR was settled by our clinical experience and needed to be verified by further studies. The intrinsic changes of oocyte from a patient with decreased OMR need to be illuminated by further studies.

In conclusion, we found that decreased OMR occurred in 1.3% ICSI cycles and 22.16% of all oocytes retrieved were immature. Primary infertility, duration of infertility, BMI, previous assisted reproductive times, number of oocytes retrieved and COH protocol were factors affecting the incidence of decreased OMR. More studies are needed to validate our results.

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Author contribution CM: project development, manuscript review. YL: data management, data analysis, manuscript writing. PY: data collection, data analysis, manuscript writing. YC: data collection, manuscript editing. JZ: project development. XZ: data analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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